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U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA)

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FEDERAL INSECTICIDE, FUNGICIDE AND
RODENTICIDE ACT SCIENTIFIC ADVISORY PANEL
(FIFRA SAP)

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REEVALUATION OF THE HUMAN HEALTH EFFECTS OF
ATRAZINE: REVIEW OF EXPERIMENTAL ANIMAL
AND IN VITRO STUDIES AND DRINKING WATER
MONITORING FREQUENCY

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The Panel convened at 8:30 a.m. in

the Hamilton Ballroom of the Hamilton Crowne
Plaza Hotel, located at 1001 14th Street,
N.W., Washington, D.C., Steven G. Heeringa,
Ph.D., Chair, and Kenneth M. Portier, Ph.D.,
Session Chair, presiding.

FIFRA SAP MEMBERS PRESENT:

STEVEN G. HEERINGA, Ph.D., Chair

KENNETH M. PORTIER, Ph.D., Session Chair

JOHN R. BUCHER, Ph.D., DABT

JANICE E. CHAMBERS, Ph.D., DABT, ATS

GERALD A. LeBLANC, Ph.D.

DANIEL SCHLENK, Ph.D.

FQPA SCIENCE REVIEW BOARD MEMBERS PRESENT:

SUSAN F. AKANA, Ph.D.

RICHARD H. COUPE, Ph.D.

KENNETH BARRY DELCLOS, Ph.D.

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ROBERT J. GILLIOM, Ph.D.

RICHARD GREENWOOD, Ph.D.

WILLIAM L. HAYTON, Ph.D.

STEVEN D. HOLLADY, Ph.D.

TERESA H. HORTON, Ph.D.

KANNAN KRISHNAN, Ph.D.

HERBERT K.H. LEE, Ph.D.

KEVIN T. O'BYRNE, Ph.D.

NU-MAY RUBY REED, Ph.D., DABT

JEAN F.L. REGAL, Ph.D.

DANIEL J. SELVAGE, Ph.D.

CARMEN J. WILLIAMS, M.D., Ph.D.

LINDA J. YOUNG, Ph.D.

ALSO PRESENT:

JOSEPH E. BAILEY, Designated Federal Official

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P-R-O-C-E-E-D-I-N-G-S

8:30 a.m.

MR. BAILEY: We've got a lot of material to cover over the next two days, and we're anxious to get going. I'm Joe Bailey. I'm serving as the DFO for the meeting, Designated Federal Official.

I just wanted to let the panel know that I tried to e-mail the public comments and presentations last night, but some of the e-mails kicked back because they were too big. What a surprise. But I will make a second attempt this afternoon or tonight to get it to everybody, so everybody has all of the presentations electronically.

At this point I'll turn it over to Dr. Portier, our Chair for this meeting. Thank you.

DR. PORTIER: Good morning. I'm Ken Portier, Chair. This is the -- I guess it's the third day of the FIFRA Scientific Advisory Panel meeting on the re-evaluation of

1 the human health effects of atrazine, review
2 of experimental animals and in vitro studies
3 and drinking water monitoring frequency.

4 We've twice introduced the panel,
5 so I don't think at this point we need to
6 reintroduce the panel. Most everyone in the
7 audience is probably familiar with us now.
8 And we have before us the bulk of our task, we
9 have remaining 12 questions, and two days to
10 do it, 16 hours. So my goal is to average
11 about 50 minutes a session, take a break after
12 two questions, and break at five o'clock this
13 evening. All right. So we're not going to
14 push it like we did yesterday. I realize
15 people have kids -- staff have kids to pick up
16 and -- yes, it's easy to keep people happy.
17 Right?

18 It's unlikely we're going to get
19 to any of the hydrology questions today, which
20 gives that part of the panel time to really
21 delve into that a little bit more. My goal
22 will be to get eight questions done today, 1.2

1 to 1.9. I'll be happy if we do that, but I --
2 you know, even if we just get through 1.8 I
3 think we'll be doing well.

4 So with that I will ask Dr. Mendez
5 or Dr. Lowit, if they have any opening
6 comments from EPA, or Dr. Cooper?

7 DR. MENDEZ: We don't have any
8 opening remarks at this time. And Dr. Cooper
9 will start reading Charge Question 1.2.

10 DR. PORTIER: Thank you.

11 DR. COOPER: I didn't know I was
12 going to do this. So the Charge Question
13 1.2 -- in Charge Question 1.2, based on an
14 evaluation of the studies examining the mode
15 of action at atrazine on neuroendocrine
16 function, Section 3.2 of the draft issue
17 paper, the Agency has preliminarily concluded
18 that atrazine affects both the HPG axis and
19 the HPA axis.

20 With respect to the temporal
21 concordance, recent studies show that atrazine
22 induces a rapid, within minutes, increase in

1 ACTH and adrenal cortical hormones,
2 corticosterone and progesterone, in both male
3 and female rats, Fraites, et al., 2009; Laws,
4 et al., 2009; and Pruett, et al., 2009, while
5 changes in the HPG axis, such as suppression
6 of the LH surge, may take up to two to three
7 days, Cooper, et al., 2009. That should be
8 2000, by the way.

9 (Laughter.)

10 DR. COOPER: Note the mistake in
11 that, please, so I'm not on the griddle to
12 produce a paper last year.

13 This sequence of HPA alterations
14 followed by HPG changes indicates that the
15 suppression of the surge may be, in part,
16 mediated by activation of the HPA axis, i.e.
17 a corticosterone suppression of the GnRH and
18 LH release. In addition, with respect to the
19 dose-response concordance, atrazine-induced
20 increases in ACTH, corticosterone and adrenal
21 progesterone are seen following a single dose
22 of atrazine, 50 milligrams per kilogram.

1 In contrast, the HPG is not
2 altered by following a single dose up to 200
3 milligrams per kilogram. However, when
4 treated for multiple days, the dose necessary
5 to alter the HPA axis is lower than or equal
6 to the one needed to affect the HPG axis.

7 Charge Question 1.2, please
8 comment on the Agency's preliminary hypothesis
9 for the mode of action involving atrazine's
10 alteration of both the HPA and the HPG axes.

11 Does the document adequately and clearly
12 describe the hypothesis in the context of a
13 toxicity pathway, i.e. cellular responses
14 that, when sufficiently perturbed, are
15 expected to result in adverse health effects?

16 Does the document clearly describe the data
17 used to test the proposed hypotheses? To what
18 extent do the available data establish key
19 events in the proposed mode of action
20 hypothesis? And what are the strengths and
21 limitations of the data available on this
22 hypothesis?

1 Please include in your comments a
2 discussion of the Agency's interpretation of
3 the data linking the initial perturbations in
4 the HPA axis to the changes in the HPG axis.

5 Is there more?

6 DR. MENDEZ: Yes, there's more.

7 Hold on.

8 DR. COOPER: Long question.

9 Please comment on the evidence that the
10 initial perturbations in the HPA axis may lead
11 to impairments in reproductive function and/or
12 developmental consequences. Which events
13 is/are viewed as critical in leading to health
14 consequences? Are there data on other
15 substances that would inform this question?

16 DR. PORTIER: Thank you. We've
17 kind of spread out the panel a little bit
18 more.

19 So, Dr. O'Byrne, you've got a
20 little of room. You ready to kick us off
21 here?

22 DR. O'BYRNE: Thank you. Thank

1 you very much.

2 I think the EPA's preliminary
3 hypothesis for activation of atrazine's mode
4 of activation -- mode of action involving
5 alteration of both the HPA and the HPG axes is
6 adequately described and scientifically sound
7 based on the experimental data that's
8 available.

9 The details of the toxicity
10 pathway, however, is very, very limited, and
11 the mechanisms of action of atrazine on the
12 perturbation of the HPG I'll describe in a
13 minute. The mechanisms of action on the HPA
14 perhaps should be moved into questions 1.3 and
15 1.4 because there's some overlap there.

16 But the key question of the causal
17 link between the activation of the HPA and the
18 subsequent suppression of the HPG axis is far,
19 far from conclusive. Nevertheless, I think
20 the available data provides a reasonable case
21 for the Agency to put forward that preliminary
22 hypothesis.

1 Now I don't wish to review the
2 post data, post-2003 data on the HPA and HPG
3 axes. I'm very mindful of the Chair's comment
4 at the beginning of this that we shouldn't
5 repeat what other people have said or what we
6 say ourselves, otherwise we'll be chopped off
7 in mid-sentence. So that's a great advantage
8 to me.

9 (Laughter.)

10 DR. O'BYRNE: But nevertheless, I
11 think Dr. Handa's additional information
12 yesterday was particularly helpful. And of
13 course you'll remember that. I would like to
14 make a very brief comment about the
15 interaction between the HPA and HPG axes, just
16 in case there are people in the audience that
17 are new.

18 It is extremely well-established
19 that there's an inverse relationship between
20 the HPA and the HPG axes, which has led to the
21 hypothesis that activation of the HPA results
22 in a suppression of the HPG. This is not

1 rocket science, and this is particularly true
2 in response to stressful stimuli. And in
3 clinical scenarios as well. For example, in
4 Cushing's disease there is a beautiful inverse
5 relationship between circulating levels of
6 cortisol and the degree of reproductive
7 suppression in terms of normal menstrual cycle
8 in women, oligo, and complete amenorrhea.

9 So this physiological correlate of
10 the inverse relationship, coupled with the new
11 evidence that atrazine activates the HP axis,
12 has obviously led the Agency to this
13 preliminary hypothesis that the mode of action
14 of atrazine involves an alteration of both of
15 these critical axes. And the influence is
16 sequential rather than some parallel fashion,
17 so that changes in the adrenal steroid
18 hormones are driving the deleterious effects
19 on the reproductive axis. So I just wanted to
20 give you that brief summary.

21 Now my major comments relating to
22 atrazine. There's clear evidence that there's

1 a transient increase in corticosterone, and
2 we've seen evidence of that with rapid
3 increase and return to baseline within six
4 hours. Whether this is measured after a
5 single injection, or exposure, or after a 28-
6 day exposure and the final administration
7 results in an indistinguishable rise and fall
8 in corticosterone.

9 Now there's ample evidence that
10 increases in -- acute increases in
11 corticosterone, cortisol depending on the
12 species, do not, and I mean do not affect the
13 pulsatile release of LH. And this is in a
14 huge range of species, from rats all the way
15 up to humans. There is, however, one
16 exception and that is the sheep. And here,
17 physiological stress levels of cortisol, or
18 cort, results in a rapid decrease in LH pulse
19 amplitude. And this happens within 30 to 60
20 minutes.

21 And this is a pituitary
22 phenomenon, where there's a reduction in

1 pituitary sensitivity to GnRH, the tropic
2 stimulus. But there is very clear, clear
3 evidence that atrazine does not have this
4 pituitary effect, and I think that data is
5 quite solid and unambiguous. And in the
6 sheep, incidentally, it also has an acute
7 effect on pulse frequency, and we don't really
8 need to go into that.

9 Now, in contrast to these -- the
10 lack of evidence of an acute effect of
11 corticol, corticosterone, on LH pulse
12 frequency, evidence concerning the effects of
13 acute stress, or cort, on the surge release of
14 LH is less consistent. However, chronic
15 levels of these hormones, their effects on the
16 surge generating mechanism are quite
17 consistent.

18 And I'd like to just talk to you a
19 little bit about the data that is available.
20 And in the context of the rat, it's actually
21 pretty meager. But, nevertheless, back in the
22 late '70s, Baldwin and his colleagues showed

1 that a single injection of dexamethasone or
2 cortisol at two to eight hours after the
3 administration of estradiol benzoate did not
4 block or affect the LH surge in rats. So
5 that's fairly conclusive that acute increases
6 in glucocorticoids do not suppress the LH
7 surge in this species.

8 However, if he takes a chronic
9 approach and implants a capsule where you get
10 chronic elevated levels of cortisol, then you
11 disturb the cycles for weeks and you
12 completely block the pre-ovulatory -- the
13 spontaneous pre-ovulatory gonadotropin surge.
14 So clearly chronic is a good example of
15 chronic cortisol having an effect.

16 Then in the mid '90s there was
17 another study where somebody restrained rats
18 for various time points, zero, one, and two
19 hours before the estimated time of the onset
20 of the spontaneous surge, and continued that
21 restraint until lights went out, which
22 basically means after the surge is over. And

1 in those rats 50 percent had no surge and 50
2 percent had an attenuation, or a decrease in
3 amplitude. So here we have two rat studies
4 that actually conflict in some ways. But you
5 can sit here and debate the reasons why that
6 may be the case.

7 I'd like to describe just a couple
8 of experiments that have been carried out in
9 the sheep, and there's been a very interesting
10 flurry of activity very, very recently in the
11 sheep, which has been initiated by one of your
12 great physiologists, Fred Cosh, who actually
13 should be here rather than me. Perhaps Joe
14 was less convincing and persuasive with Fred
15 Cosh. I don't know. But, well, maybe he's
16 enjoying his retirement.

17 But he really has spurred the
18 sheep people interaction around the globe.
19 And, in particular, Harry Dobson in Liverpool
20 in the UK, and what she's done is that she's
21 acutely activated the HP axis in her ewes with
22 insulin-induced hypoglycemia. And she's done

1 this at 30 and 32 hours after withdrawal of
2 progesterone. What the sheep guys do is they
3 have their sheep, they put an implant of
4 progesterone in and then they pull it out, and
5 then 48 hours later you have a spontaneous LH
6 surge. And this is synchronizing the surges
7 so to -- it facilitates their experimental
8 design.

9 So she induced hypoglycemia, and
10 very close to the surge. It decreased
11 circulating levels of estrogen significantly,
12 but not markedly. And this resulted in a
13 delay of the LH surge by nine hours. What
14 Fred Cosh has done, and this was published
15 this year, Fred Cosh has also done an
16 experiment, but instead of using a single
17 acute stress, he's used a series of acute
18 stresses, and these are psychological
19 stresses. And he's exposed his ewes to thee
20 psychological stresses at 12 to 18 hours, 24
21 to 30 hours, and then 36 to 42 hours after
22 that progesterone implant is pulled out.

1 Remember, the surge occurs at 48 hours.

2 And that repeated acute stress
3 paradigm, and he had a whole range of these,
4 I've just described one of them, had
5 absolutely no effect on the LH surge. It
6 occurred on time, normal amplitude. So here
7 we have two sheep people had papers published
8 this year that also are very, very different.

9 But what Fred did is, if he
10 administered physiological levels of cort,
11 corticosterone, for 42 hours, then he delayed
12 the LH surge by 10 hours, just like Harry
13 Dobson. And there's also a reduction in
14 amplitude. But you've got to remember that
15 the sheep is quite unusual in this context of
16 amplitude modulation in response to
17 physiological levels of cort.

18 I think I'd also like to remind
19 the panel that there isn't a shred of evidence
20 that the GnRH surge generating mechanism in
21 the rat, or indeed the sheep, bears any
22 resemblance to a human or primate, and I think

1 that's actually very important. And we can
2 discuss that if people think that's necessary.

3 So how does atrazine fit into all
4 of this? Well, although there is clear
5 evidence that sustained or chronic levels of
6 glucocorticoids suppress the pulse generator,
7 and I hope that's fairly clear, in a wide
8 range of species, from rats right up to
9 humans, there is a lack of evidence that
10 atrazine causes a sustained increase in
11 corticosterone.

12 Indeed, if you look at the data
13 that was presented in the last couple of days
14 from Pruett published in 2009, daily exposures
15 to astronomical levels of atrazine, we're
16 talking about 150 milligrams per kilogram per
17 day given intraperitoneally, resulted in a
18 transient increase in cort that was no
19 different from that from a single injection.
20 So up and down within six hours.

21 Dr. Handa showed us yesterday that
22 50 milligrams per kilogram increased

1 corticosterone for less than an hour in the
2 rat. The other study was in the mouse. So
3 the notion that a three-day protocol of
4 exposure to 50 milligrams could result in a
5 complete blockade of the LH surge, I think is
6 unlikely. And then the sort of clinch was
7 yesterday again, when Dr. Handa showed us that
8 adrenalectomy didn't block the surge
9 induced -- the blockade of the surge induced
10 by atrazine. So I think that really does make
11 one appreciate that the glucocorticoids
12 perhaps are not involved.

13 With respect to the health
14 consequences, it's my considered opinion that
15 there is little evidence, perhaps no evidence,
16 of adversity because the concentrations that
17 have been used in the various experiments that
18 I've reviewed draw no comparison whatsoever to
19 what we would expect humans, or indeed
20 wildlife, to be exposed to.

21 This may -- it may be very
22 different for amphibians. I mean these guys

1 live in the water. They're like a blancmange;
2 they absorb everything through their skin, and
3 very readily. And I think this was elegantly
4 portrayed yesterday by Pastoor's comments.
5 That's my opinion.

6 I think there is a dire need for
7 new data, particularly experiments involving
8 environmentally relevant doses of atrazine,
9 given chronically, via an oral route, and I
10 don't mean by gavage, I mean in their drinking
11 water. And it astonishes me and some of my
12 other colleagues here that nobody's actually
13 looked at the effect of such administration of
14 low levels that one would expect animals to be
15 exposed to, and looking at the effects on
16 corticosterone release, basal corticosterone
17 release. It's not been done, and that is
18 absolutely mind blowing. That's the first
19 experiment that I would have done, and in
20 those same animals you could have looked at
21 various physiological reproductive parameters.

22 And I think the comment that Dr.

1 Gilliom made yesterday about concurrence is
2 very, very well taken. And he simply added to
3 the bottle of water. So that's easy. Now Dr.
4 Mendez described key additional experiments
5 and data that's going to come out in spring
6 and summer of 2010. Well, spring's here and
7 it feels like summer's here as well, to me,
8 coming from London. But, you know, some of
9 those are critical and I'm wondering when
10 they're going to come.

11 But I cannot impress the
12 importance of looking at brain expression of
13 critical neuropeptides. I mean the fact that
14 nobody's bothered to look at CRF and
15 vasopressin expression is again astonishing.
16 Looking at GnRH levels by microdialysis is
17 something that I think should be done, and
18 there's somebody sitting around this table who
19 is an expert in this, and this is not a
20 trivial technique, as very few people can do
21 it properly. And you've got somebody in your
22 presence who can do this beautifully. So

1 people should take advantage of that.

2 And the catecholamines. I mean
3 one can't escape from those. And then
4 kisspeptin, I mean Dr. Mendez mentioned this
5 in her slides. Kisspeptin's been around for
6 something like seven years. It's the new
7 thing on the block in terms of for the
8 reproductive physiologists, and it's the
9 driving force to the GnRH neurons. And,
10 again, nobody's bothered, as far as we can
11 tell, to look at the expression of kisspeptin
12 in response to this herbicide. And these are
13 very simple and easy experiments to do, and
14 would give us a huge amount of information
15 that would make us -- make it easier for us to
16 give an informed decision.

17 So I think that's all I wish to
18 comment in my response.

19 DR. PORTIER: Thank you.

20 Dr. Bucher.

21 DR. BUCHER: Thanks.

22 John Bucher. So, in general, I

1 thought that the document adequately
2 established the interrelationships between
3 disruption of the HPG axis and the resulting
4 phenotypic effects including reproduction,
5 development, immune endpoints, and cancer in
6 experimental animals. There's a general
7 consistency in dose, response, and timing that
8 are required to satisfy a mode of action, and
9 the document does a reasonable job of
10 interpreting the recent literature in the
11 context of the proposed MOA.

12 In my opinion, more could have
13 been said about the biological plausibility
14 and support for cross-species applicability
15 that the literature on the HPA axis and stress
16 research in general that you just heard about
17 brings to the proposed MOA. Although I'm not
18 an expert at all in this area, the human
19 relevance of using disruption of the LH surge
20 and the benchmark dose calculation is, in my
21 mind, strengthened by the extensive
22 documentation of effects of various types of

1 stress acting through the HPG axis to affect
2 human reproductive health.

3 That said, I don't believe that
4 figure 3, which is the schematic of the
5 proposed MOA on page 30 of the white paper,
6 does a good job of capturing the key events in
7 the proposed MOA. The problem is that it goes
8 into too much detail in trying to describe
9 what are, in essence, redundant mechanisms
10 that are typically involved maintaining
11 homeostasis.

12 This also relates to the question
13 of whether there's a clear toxicity pathway
14 described in the document. Although Dr.
15 Cooper, on Monday, said he was leaning towards
16 the right side of the house through the HPA
17 axis as representing a direct or possibly a
18 linear pathway for atrazine's biological
19 effects.

20 I don't think that these highly
21 dynamic mechanisms really lend themselves to
22 the toxicity pathway concept. For example, LH

1 secretion is directly sensitive to
2 gonadotropin-releasing hormone, but also
3 indirectly to gonadotropin-inhibiting hormone,
4 ACTH, corticosterone, corticotropin-releasing
5 hormone, and possibly progesterone.

6 It is not clear why, to me yet,
7 why the data on temporal relationships between
8 the stimulation of the HPA axis and the
9 disruption of the HPG axis are what they are.

10 I think it may be more useful to scale back
11 your expectations for making all of the data
12 fit within a coherent framework. Toxicity
13 pathways most likely are not linear, but
14 rather are webs with nodes that represent
15 convergent points, or points of greatest
16 sensitivity. Figure 3, to me, is really a web
17 with LH pulse suppression as a sensitive node.

18 Despite this, I think the Agency's
19 on solid ground in using disruption of the LH
20 release and other biological endpoints that
21 have been directly associated with it as
22 measurable key events. This endpoint is the

1 most sensitive in terms of the atrazine
2 chronic dosing studies and it's been plausibly
3 linked to the phenotypic outcomes of interest.

4 As with the application of other
5 MOAs to specific situations, if you look
6 closely at how well the MOA fits specific data
7 sets, you'll see weaknesses in fits to the
8 model. But as we've all heard many times, all
9 models are wrong, but some are useful. I
10 think in this case the disruption of the HPG
11 axis is useful and the Agency should move
12 forward with it as a point of departure until
13 something clearly better comes along.

14 That concludes my comments.

15 DR. PORTIER: Thank you.

16 Dr. Akana?

17 DR. AKANA: What I'll do is just
18 add what has not been covered already, and I
19 concur with quite a number of the points. In
20 my opinion, the hypothesis, like many, is a
21 maturing hypothesis, and I don't think it's
22 quite developed to the point where it should

1 be aggressively pursued at this point.

2 Now what do I mean? One of the
3 points of the hypothesis is that there is a
4 central action of atrazine, and here is where
5 I think some important spotty sets of data are
6 missing. And when we talk about central
7 action, we're not talking about the brain, and
8 the type of evidence we've had so far is,
9 again, a little bit lighter on what you find
10 in the brain.

11 I think it's very promising that
12 we heard some of the cFos data and some of the
13 gonadotropin -- excuse me, the GnRH brain
14 data, but I think it's absolutely critical
15 that in the same kinds of animals they also
16 look at CRF and ABP in those brain sections.
17 And if they also layer in there with cFos, you
18 can get some sort of temporal sense of which
19 one is reacting first. So that part, I think,
20 is critical.

21 Now when we talk about the
22 activation of HPA system, there's the

1 hypothalamus, so that is relatively untouched.

2 The data on pituitary, POMC type of

3 production, that's also very lightly touched.

4 But what most concerns me when you talk about
5 activation of the HPA system; it is a feedback

6 system, a negative feedback system. And the

7 very preliminary data that we've have, which

8 is really exciting, that Dr. Handa talked

9 about with the adrenalectomy, is the direction

10 I think the studies need to go.

11 What we've seen are some really
12 lovely datasets on characterizing the response

13 to the HPA to atrazine in terms of ACTH and

14 corticosterone. And the data sets are

15 strongest with a single injection, a single

16 acute injection. The time frame and the dose

17 response and the time domains are very nice

18 for saying that atrazine stimulates the HPA

19 system with a single acute injection.

20 Now, the other fun thing about the

21 HPA system is with one of the outputs, just

22 one of them, which is corticosterone. As we

1 all remember, corticosterone is also a
2 glucocorticoid, and that is a hidden partner
3 in the hypothesis that must be addressed.
4 Because it's a glucocorticoid, you're changing
5 metabolism. Okay. In the framework of an
6 acute response, that is actually not a major,
7 major concern.

8 But as soon as you move into a
9 chronic model, a chronic model of atrazine,
10 you enter a whole new type of dynamic. What
11 has been emerging in the last 10 years is in
12 the stress system, when you move into repeated
13 or chronic stress, you have a different brain.
14 Okay. CRF and PVN, that one is pretty well
15 recognized, but CRF is found in other cell
16 bodies, cell brain nuclides in the brain.
17 It's a distributed system, it's responsive to
18 stress, they interact. There are neural
19 connections that are proven, and they have
20 major, major outputs.

21 So you have CRF and PVN, but you
22 also have it in BNST, in the central nucleus

1 of amygdala, you have in the prefrontal
2 cortex. And when it's activated in a stress
3 circuit, what you get is actually positive
4 feedback of corticosterone onto those systems,
5 and it drives other behaviors. So you have a
6 different kind of animal, which -- with
7 chronic stress, and it might help make some of
8 the data in the repeated atrazine application
9 much more coherent when you are sensitive to
10 that.

11 Now when we talk about
12 glucocorticoids and the metabolism, this is
13 one of my areas of energy balance, you are
14 feeding into the reproductive system. The
15 reproductive system is sensitive to energy
16 substrate flows. So I would urge a more -- a
17 larger picture taken with the data, that you
18 look not only on the HPA and the LH surge, but
19 in the framework of what kind of energy peak
20 the animal is. For instance, atrazine very
21 often reduces body weight.

22 And now, in terms of the animal

1 and negative energy balance, this is critical
2 how it nuances some of the LH surge and also
3 the HPA. So what I'm saying is, I think the
4 hypothesis needs to evolve to address the
5 acute response somewhat separately from the
6 chronic response.

7 That was my major point. I also
8 would like to table the toxicity pathway to
9 the next charge question. I think the key
10 events are still somewhat murky, therefore, in
11 this change because we don't know precisely
12 what's happening, the atrazine action, as it
13 kicks off in the hypothalamus.

14 Now the idea that it works
15 primarily on the HPA is perhaps conditioned,
16 because the literature shows there is, again,
17 a very strong interaction in the chronic state
18 between the HPA and the HPG. And there's some
19 very nice models of where HPA and HPG axes are
20 rendered independent of each other by
21 controlling both the corticosterone level and,
22 in the male rat, the testosterone level.

1 And here I'm thinking of a model
2 of Victor Viau, and I think that is a fabulous
3 template to consider how to interpret atrazine
4 action when you have independent control of
5 each axis. So overall, I think the strength
6 of the hypothesis is mostly in acute
7 injection -- in acute atrazine exposure. I
8 think it's much more limited in the chronic
9 state, and I think there are many tools that
10 can -- that are in place already and well-
11 established that can be used to tackle those
12 problems, and I would urge the panel to
13 encourage those be employed.

14 And I'll stop there. Thank you.

15 DR. PORTIER: Thank you.

16 Dr. Fenner-Crisp?

17 DR. FENNER-CRISP: Given what's
18 already been said, I don't want to repeat any
19 of that. I support most of the comments made.
20 I'd like to focus mine on exposure route and
21 its relevance in dose concordance. I can
22 appreciate that in the laboratory setting one

1 wants to do experiments that see something,
2 and that generally can explain why higher
3 doses are used, at least in the first round.
4 But I also would appreciate, as Dr. O'Bryne's
5 comment, one wants to ultimately understand
6 what may or may not be happening at human
7 exposure relevant levels.

8 The body of literature in vivo
9 show studies by several routes, oral gavage,
10 some sub-Q, some IP, and one would have to try
11 to understand what difference does that make
12 in the results in comparing them across those
13 studies with respect to pharmacokinetics.
14 Would you be seeing different patterns of
15 percentages of rate and percentages of
16 metabolic formation, and conjugation, the
17 whole ADME scheme, depending upon the route-
18 specific application?

19 And how does that affect the
20 results that one sees and how does one take
21 that into account when trying to do a dose
22 concordance across these varying routes of

1 exposure, trying to compare and understand
2 their relationship, particularly when trying
3 to understand where, how, if the HPA axis
4 disturbances impinge on the HPG.

5 The Agency mentioned somewhere in
6 the white paper that they plan to do benchmark
7 dose analysis somewhere along the way when
8 they get to the hazard characterization. It
9 may be useful to do that sooner rather than
10 later to get a better understanding of dose
11 concordance in hazard identification.

12 And I am assuming that one's going
13 to apply somebody's, not the Agency's, pre-
14 existing PBPK model to expand on that
15 understanding. That would be a recommendation
16 that I would offer.

17 I think that it may come to the
18 point where some of the studies that have been
19 done, and offer some kind of results, may have
20 to be redone by more relevant routes of
21 exposure to confirm or not those particular
22 findings, if at a point in time they are

1 thought of as being critical to the
2 understanding of the pathways, and an integral
3 part in doing the risk assessment.

4 DR. PORTIER: Thank you.

5 DR. SELVAGE: Okay. Thanks.

6 My response is -- it kind of
7 segues into the next question as well, so I'll
8 keep this part pretty limited. I agree with
9 most of what's been said. I think Dr. O'Byrne
10 did a really nice job of describing, you know,
11 a lot of concerns that I think are valid. You
12 know, I guess I'll just add that, you know, I
13 do think the document does describe the
14 hypothesis well; I think that's clear.

15 However, I don't think there's
16 nearly enough data yet to, you know, draw the
17 conclusion that the EPA is leaning towards, in
18 that it's the HPA axis disruption that's
19 affecting the HPG function. You know, I would
20 say that, you know, in thinking about this
21 from a CNS perspective, you have -- there's a
22 lot of overlap between the HPA and the HPG

1 axis at the level of the CNS in terms of, you
2 know, receptors for gonadal hormones being
3 present in areas that are going to affect HPA
4 axis function, and vice versa. So I think,
5 you know, it's going to be important to look
6 at that.

7 Also, a lot of stimuli that are
8 going to affect the HPA axis are also going to
9 affect the HPG axis is what I'm trying to get
10 at here, so, you know, perturbations of a lot
11 of neurotransmitter systems that are going to
12 affect the HPA axis are also going to affect
13 the HPG axis, you know, and they might be
14 doing this -- affecting each axis separately.
15 So I think, you know, you could be having some
16 other central action affecting both of these
17 systems. So I think it's really important to
18 look at what's going on at the level of the
19 brain in much more depth.

20 Also, I need to concur with Dr.
21 O'Bryne on the need for more cort
22 measurements, basal cort measurements, in

1 particular, and to my mind this is especially
2 important in the chronic studies because all
3 the cort measurements that we've seen have
4 been after atrazine in the chronic studies.
5 You know, there's certainly a possibility
6 that, for one thing, the circadian rhythm of
7 cort could possibly be disrupted by atrazine.

8 Also, you know, it seems possible
9 to me that you have up-regulation of the HPA
10 axis in general in these females. It's
11 certainly a possibility. I think that needs
12 to be tested, for instance, give atrazine, you
13 know, chronically then stop the atrazine and
14 on the next day give another stressor and see
15 how their response compares to, you know,
16 animals that haven't received atrazine, I
17 think, if you want to see if you're getting an
18 up-regulation in general of the HPA axis.

19 I think there's, you know, some
20 possibilities with, you know, the proposed
21 mechanisms of action, for instance the
22 phosphodiesterase inhibitors, the increased

1 cyclic AMP, and cyclic AMP for instance is --
2 cyclic AMP pathways are involved in the --
3 stimulating the transcription of CRF. So I
4 think looking at those areas will be
5 important.

6 Other than that, I think a lot of
7 this will just feed into the next question.
8 You know, I think there's a good -- you have
9 a good starting point, but I think a lot more
10 needs to be done to draw a firm conclusion.
11 Right now the conclusions are being based on
12 correlations, and obviously correlation
13 doesn't mean causation. So I think at that
14 point we could probably go on to the next
15 question and let -- well, after other comment.

16 DR. PORTIER: Thank you. At this
17 point we'll open it up to comments from anyone
18 on the panel.

19 Dr. Krishnan. Was it -- oh, Dr.
20 Akana.

21 DR. AKANA: I wanted to reinforce
22 a point that Daniel made, is that in a lot of

1 the timing of samples taken, it's like 15
2 minutes or 30 minutes, and I totally
3 appreciate why that's done, particularly if
4 it's a terminal sample. But ACTH actually has
5 a much, much faster time dynamic than
6 steroids. It's up and down, so in terms of
7 like restraint, it responds in under two
8 minutes, and in our hands it's down in like 15
9 minutes. It's fast. But what it does
10 stimulate, of course, is a longer, slower and
11 sustained rise in corticosterone.

12 So in the experiments we see,
13 particularly with cannulated animals, the
14 opportunity to take samples that are sensitive
15 around the peaks and falls of where you're
16 going to find ACTH separate from
17 corticosterone are just wide open and can be
18 taken to advantage.

19 And then I'll take this point to
20 say that the urine collection and measurement
21 of corticosterone, to my mind, is a fabulous
22 tool. And what it brings to mind also is to

1 recall that corticosterone is carried by a
2 binding protein. When you measure
3 corticosterone you're actually, in most cases,
4 measuring total. But the bioactive portion,
5 of course, is free. So you have to
6 reinterpret this, particularly in a chronic
7 state where the binding protein will decrease.

8 And the urine samples are
9 fabulous, again, because they give you an
10 integrated measure, but you're measuring free
11 corticosterone, the bioactive fraction being
12 seen. So there's a lot of rich possibilities
13 in the kinds of data that are coming out, but
14 they could be tweaked, be a bit more
15 sensitive.

16 DR. PORTIER: Dr. Krishnan, and
17 then Dr. Hayton.

18 DR. KRISHNAN: I just wanted to --
19 to O'Bryne's comment in relation to those two
20 slides yesterday. You saw some of the
21 magnitude of difference between the NOAEL
22 water concentration sources and the monitored

1 concentrations. I think that's what you were
2 referring to at some point.

3 Just look at the last one, or the
4 one to the right-most comparison, which was
5 the chronic one. There was a factor of about
6 6,000-something, where the NOAEL is all the
7 way up there, NOAEL water concentration,
8 monitored community water concentration was
9 here, and the factor was about 6,000-
10 something, 6,200 or 500, whatever.

11 The classification I was trying to
12 get when you all walked out on me at the end
13 for the session there --

14 (Laughter.)

15 DR. KRISHNAN -- was that the
16 expected factor, or the target factor is
17 5,000. That's what wasn't on the figure. The
18 difference was being shown as 6,000-something.
19 But the expected or the target factor in the
20 risk assessment was about 5,000. That was my
21 comment yesterday.

22 Because of the uncertainty factor

1 on the source contribution that's accounted
2 for in the NOAEL to bring it down to a human
3 relevant concentration. So that would make a
4 difference. Because down below is what
5 actually the humans are consuming as water
6 concentration. Up there is you take the dose
7 given to the animal and then try to solubilize
8 them in the water that can be consumed.

9 So, you know, that -- I just
10 wanted to clarify that. So I'm trying to --

11 DR. LOWIT: Kannan? Dr. Krishnan?

12 DR. KRISHNAN: Yes.

13 DR. LOWIT: We had some questions
14 about Dr. Pastoor's slides also, about the
15 differences in some of the numbers. But
16 the -- but one thing that I know to be true is
17 that the -- whether -- the magnitude of the
18 totality of the uncertainty factors is not
19 5,000, and that's the value that I think that
20 you're quoting. It's either 300 or 1,000 --

21 DR. KRISHNAN: Okay. Well, the --

22 DR. LOWIT -- depending on the --

1 DR. KRISHNAN -- 5,000 I quoted is
2 based on what he presented. He said 1,000 was
3 the factor involved in that particular
4 assessment, including a 10 for children. And
5 then he said 20 percent was included as a
6 source contribution. That was presented
7 during his talk, and then there was some other
8 comments --

9 DR. LOWIT: Yes, and --

10 DR. KRISHNAN -- that came after.

11 DR. LOWIT -- too bad Dr. Pastoor
12 couldn't clarify those numbers with the
13 microphone on, because I think some of the
14 numbers he was quoting, I think they were
15 getting mixed up, and there was some
16 differences in between the OW and the
17 Pesticides Office procedures that got blended
18 in that conversation. It's really confusing.

19 DR. KRISHNAN: Yes. No, so I just
20 wanted to, you know, keep in that mind. I
21 didn't want that to be one of the driving
22 forces of our discussion, or how you view

1 things.

2 The other thing is that the focus
3 on the toxicity pathway is based on the
4 National Academy of Sciences recommendations,
5 and is unquestionably on a solid footing the
6 way the Agency has put it together. But one
7 of the things that worries me a bit is that I
8 hope there -- the assessments won't take us
9 down a pathway of establishing no observable
10 perturbation effect level without, you know,
11 regard to the no observable address effect
12 level.

13 So I think at some point as this
14 matures along, that relationship has to be
15 strengthened and clearly presented, such as a
16 like an AUC of an LH surge works in an
17 organism level effect or something, so that
18 the perturbation levels for specific pathways
19 that are chosen, even though, you know, some
20 are blurred along the line with respect to the
21 outcome in the animals.

22 As long as those are chosen for a

1 benchmark, those analyses or other kind, with
2 particular reference to, or in relationship to
3 the organism that will affect. I think that
4 will be reasonable. I just wanted to add that
5 comment.

6 DR. PORTIER: Dr. Hayton?

7 DR. HAYTON: I have a question for
8 the discussion, and I'm trying to understand.
9 I know we can measure perturbations in the
10 HPA/HPG axis signals, at what point do you
11 think those constitute an adverse health
12 effect? I mean me speaking into this
13 microphone, my corticosterone probably is
14 going up, but is --

15 (Laughter.)

16 DR. HAYTON -- is that an adverse
17 health effect? And it seems to me there's not
18 much linkage between all those signals and
19 adverse health. And I ask this because it's
20 important for a later question, so maybe it
21 gets addressed in later questions too, but any
22 perspective on that?

1 DR. PORTIER: Dr. O'Byrne?

2 DR. O'BYRNE: I think acute
3 effects are not important. I think there's
4 ample evidence of that. But chronic elevated
5 levels are putting you at risk, and there's
6 huge amounts of clinical data for that in both
7 men and women in terms of infertility and the
8 inverse relationship.

9 However, whatever method you use
10 to reduce those stress levels, whether it's
11 cognitive behavioral therapy, talking to women
12 and just giving them a nice environment to
13 relieve their tensions, et cetera within --
14 for example, within fertility clinics, you can
15 restore fertility quite easily. I mean,
16 again, there's some magnificent data coming
17 out of the US from Sarah Berger's lab where
18 you can get an 80 percent restoration of
19 normal fertility through a short course of
20 cognitive behavioral therapy. I mean it's
21 just mind-blowingly astonishing data. So
22 chronic levels, yes, are a problem.

1 DR. PORTIER: Dr. Regal had her
2 hand up, and then Dr. Selvage, and then Dr.
3 Williams.

4 DR. REGAL: Just a quick comment
5 in terms of Dr. Pruett's data where he showed
6 that there were alterations in immune system
7 function that correlate -- or immune system
8 parameters that correlated with area under the
9 corticosterone curve. So that under his
10 situations where he was dosing the animals,
11 there was some function change.

12 DR. SELVAGE: Dr. Selvage. I
13 concur with that. I just wanted to add that,
14 you know, it definitely is the chronic
15 activation of the HPA axis that you want to
16 worry about, and there's just a huge laundry
17 list of problems associated with that,
18 including immune system dysfunction, also
19 reproductive dysfunction, psychological
20 disorders, et cetera. So I think that is what
21 we should be mostly concerned about, if we're
22 going to be concerned.

1 DR. PORTIER: I think Dr. Lowit
2 wanted to slip in before Dr. Williams.

3 DR. LOWIT: Yes, we have -- Ralph
4 and Dr. Cooper and I were just, I think at the
5 same time, having the same question, and it
6 may not go here. As I've scanned the
7 questions, it may actually go in 1.9, but I'm
8 going to ask it anyway because it's relevant
9 to the discussion.

10 The discussants are talking about
11 acute and chronic. Where do you turn the --
12 where does -- you turn from acute to chronic,
13 and keeping in mind what our needs are here,
14 to define some temporal window to establish
15 regulatory limits. So what do we mean as
16 chronic, and when we go from a whole bunch of
17 acutes to something that becomes chronic?

18 DR. PORTIER: So we'll keep that
19 question in mind, as Dr. Williams come in.

20 DR. WILLIAMS: I just would like
21 to ask for clarification on the discussion
22 with Dr. Krishnan and Dr. Lowit. I didn't

1 understand what you were getting at terms of
2 the 5,000 and 1,000, and what do you really
3 mean, like for the more lay person in that?
4 Do you mean that the doses used are even
5 higher than they ought to be, or should the
6 relevant doses be lower, or what --

7 DR. LOWIT: Well, if you remember
8 from Dr. Pastoor's series of slides, what he
9 was doing in those slides was to compare the
10 atrazine in drinking water monitor levels that
11 Syngenta has calculated with their box and
12 whisker plots across different durations. So
13 basically what Dr. Pastoor was trying to do in
14 a couple of slides was to put everything that
15 we're talking about in a risk assessment
16 context, in bullet form that was quick.

17 And it's -- there's enough nuance
18 in the differences there that there's life
19 stage, there's time, there's different
20 offices. He had things on there that come
21 from the Pesticides Office and from the Water
22 Office, and so it was a blend of a lot of

1 different things on one slide, and he just
2 didn't have time to really go through and
3 explain what all of the columns were. And so
4 in the haste, it just got really quick,
5 because everyone was tired.

6 So what he was doing in that
7 series of slides, and I don't want to speak
8 for him, but I think this is what he was
9 doing, was to compare different aspects of
10 what goes into a risk assessment to the water
11 monitoring data as a reality check, as a
12 reality check to see how the doses in the
13 animal studies compare to what humans get in
14 the water, and actually US water monitoring,
15 and to -- I believe his point was to show that
16 the magnitude between what's in the animal
17 studies that's used as that line in the sand
18 versus what's in the monitoring data are
19 pretty large differences in there.

20 But what got lost in the speed was
21 the nuance of how the uncertainty factors are
22 used, how the conversation from a milligram to

1 a kilogram to a ppm is done across different
2 life stages. So I think that's where a lot of
3 the confusion has been of how some of those
4 numbers were derived.

5 DR. WILLIAMS: So if you take sort
6 of the number of the animal exposure that's
7 closest to some adverse affect in any life
8 stage in humans, is there anything that's
9 closer than something like 100,000 that he was
10 talking about? Like at what point are we --
11 like how far off are the animal studies --

12 DR. LOWIT: Oh, it's much
13 closer --

14 DR. WILLIAMS -- from any possible
15 risk to humans?

16 DR. MENDEZ: It's closer to
17 100,000 --

18 DR. LOWIT: Nelson Thurman's going
19 to come up here.

20 DR. MENDEZ: If you could just
21 give us a second. But I just wanted to add to
22 what Dr. Lowit was saying in terms of the

1 uncertainty factors. When the Office of
2 Pesticide Programs calculated drinking water
3 level of comparison, we consider the body
4 weight of the individual drinking, for adults,
5 two liters of water. The Office of Water does
6 it slightly different with a 20 percent
7 contribution coming from the water. So that's
8 where the difference between the health
9 advisory levels and the DWLOCs come in.

10 DR. LOWIT: And it's further
11 complicated by the MCL comes from a fairly old
12 dog study whereas all the Pesticides Office
13 work comes from the mode of action that you've
14 heard quite a bit about. Not the HPA part but
15 the HPG part.

16 DR. PORTIER: Instead of kind of
17 going off on this, Carmen, maybe at the break
18 we'll sit down and let you explain how they
19 kind of use uncertainty factors and clarify
20 it. But I think most of the panel probably
21 understands this? No? Okay. I just wanted
22 to double check.

1 (Laughter.)

2 DR. PORTIER: So we'll take two of
3 you because -- no, I know Ken Delclos knows
4 this. Okay. Well, then I stand corrected.
5 Continue.

6 DR. LOWIT: It might actually make
7 more sense if we want to either have Dr.
8 Pastoor explain it himself, or alternatively
9 a group of us from the Agency can, at the
10 break, throw a slide together of what some of
11 the pieces are --

12 DR. PORTIER: Why don't we do
13 that.

14 DR. LOWIT -- if that would help?

15 DR. PORTIER: Dr. Horton?

16 DR. HORTON: No, all we're really
17 trying to get is a sense -- we don't need a
18 detail, we're just trying to get a sense of
19 how close we are to safe versus unsafe as we
20 go -- as we look at those box and whiskers
21 relative to what --

22 DR. LOWIT: That's not a two-word

1 answer. It's --

2 DR. HORTON: Okay. Okay.

3 (Laughter.)

4 DR. PORTIER: I'm going to ask Dr.
5 Greenwood to step here for a minute, because
6 he's usually pretty good at explaining stuff.

7 DR. GREENWOOD: I don't want to
8 try and explain, I think we need to get
9 this -- I think it is important because we've
10 already heard about, from several people,
11 about the importance of pharmacokinetics, and
12 that's something the three of us here have
13 been discussing on and off looking at the
14 papers.

15 It's not straightforward to
16 interpret them, and I think it is important
17 that everybody understands the relevance of
18 the levels in the water compared with the
19 probable or possible adding under the curve in
20 the plasma. We want to try and relate what
21 levels of dose given to the animals gives you
22 those areas and what sort of concentrations in

1 the water are giving what sort of exposure in
2 the gut to humans. So in order to sort this
3 out, I think we all need to be clear about
4 what's going on here.

5 DR. PORTIER: My question is, is
6 this the question to be doing it on?

7 DR. LOWIT: That's for, I think,
8 for you to judge as the Chair. But if it's
9 going to cause at least certain numbers of the
10 panel to struggle through the responses to
11 some of the questions, I think at the break
12 we -- that, you know, that the Agency takes,
13 you know, an extra five minutes and we throw
14 something together to help you understand a
15 little bit more of the risk assessment
16 process. But otherwise, I think the better
17 place in 1.9, but that may be tomorrow.

18 DR. PORTIER: No, I think we
19 should do it today, but I'm just trying to
20 figure out whether in this question, which
21 has, you know, six very specific questions,
22 we're king of getting side-tracked, and I

1 don't want to get too side-tracked on that.

2 Dr. Krishnan.

3 DR. KRISHNAN: I think one of the
4 reasons for the side-track being whether the
5 doses we are talking about are really out of
6 whack or is there any relevance at all,
7 because with some of the thousands of factors
8 we saw, I think that's where we got a bit
9 confused.

10 If I can take you all -- I'll only
11 take two seconds -- page number 5 of Pastoor's
12 presentation, if we can get back to that,
13 that's where the factor is. Well, if you can
14 find that, and we can --

15 DR. PORTIER: That's what I was
16 thinking, if EPA could bring that up after the
17 break, we'll have a 10 minute presentation by
18 EPA so they can clarify that. How about that?

19 DR. LOWIT: Yes, we may have to
20 make our own version of that one, because we
21 weren't sure about some of what was -- it was
22 just a confusing presentation. We just have

1 our own version, if that's okay?

2 DR. PORTIER: That's fine.

3 DR. LOWIT: I hope Nelson's going
4 help.

5 DR. PORTIER: Okay. So we'll come
6 back to that and, you know, we'll clarify that
7 definitely today, before lunch.

8 Okay. So if we can get back to
9 these questions. Where are we? Dr. Akana.

10 DR. AKANA: So, when you talk
11 about what are the health concerns of acute
12 and chronic for a single administration of
13 atrazine that's not pharmacological, in the
14 adult I don't think there are major health
15 consequences to a single exposure. In the
16 adult. And then later in the session we'll be
17 talking about doses given to prenatal or
18 gestational or pubertal animals, and that's a
19 whole different ball of wax.

20 In terms of the chronic measures,
21 the problem with looking at what are the
22 health outcomes on chronic exposure is you

1 have a wealth of endpoints to look at, all
2 with different time domains. So you could
3 pick one, any one. You could pick
4 reproductive, immune, body weight, which is
5 one of my favorite cheap endpoints, and what
6 I would imagine is, will you hypothetically
7 want that water exposure chart that we've
8 talked about, and floating above it you want
9 outcomes.

10 What is the first -- what are the
11 responses of the animals to the LOAEL? You
12 know, how major are we talking about, a
13 thousand-fold response in the animal, you
14 know, what's our concern here. So while we
15 construct the water one, what we've one day
16 want to work towards is a hypothetical outcome
17 box and whisker diagram floating right above
18 the water.

19 DR. PORTIER: Dr. Selvage.

20 DR. SELVAGE: Yes, I just wanted
21 to make a couple of comments regarding this
22 issue, one being atrazine -- personally I'm

1 not so concerned about atrazine levels in the
2 plasma, per se. You know, this is stuff
3 that's going to get into tissues, you know,
4 I'll get -- it gets into the brain, et cetera.
5 And if I remember correctly, it hangs out in
6 the brain for some time. I don't think it
7 gets metabolized in the brain very quickly, so
8 I think we need to be concerned about levels
9 in the brain, et cetera. I think that's
10 important when you're talking about this
11 issue.

12 The other comment I wanted to make
13 regarding chronic versus just acute HPA
14 activation is we almost have to have two
15 discussions, one concerning males and one
16 concerning females because of the lack --
17 supposed lack of habituation you see in
18 females.

19 DR. PORTIER: Any additional
20 comments on this? This is really good. The
21 problem with the first question is we always
22 want to put everything under the first

1 question, and I'm trying to avoid that. I
2 think -- you know, I've heard a lot of good
3 comments from this.

4 Dr. O'Byrne, did you get good
5 notes on this? You think you're going to be
6 able to write up this first one?

7 DR. O'BYRNE: I'll borrow yours.

8 DR. PORTIER: I don't have -- I
9 have three of these -- oh, right yes. Yes, I
10 was going through your six questions; I think
11 they've answered -- we have answers to your
12 six components of this first question. It
13 seems that there is some agreement,
14 concurrence with the hypothesis, but there's
15 things around it that the panel wants to fill
16 in with your model. I guess that would be a
17 fair thing to say.

18 Anna?

19 DR. LOWIT: I think we'll sort of
20 hold back any other clarification questions
21 till we hear the next couple of questions
22 because I think combined we may have a

1 clarification or two.

2 DR. PORTIER: Okay. With that I
3 think we'll move on to Question 1.3, which is
4 another multi-part question.

5 DR. LOWIT: And, Joe, if you could
6 come do your --

7 DR. PORTIER: Magic.

8 DR. LOWIT: But I'll read from the
9 paper copy, I guess.

10 DR. PORTIER: By the way, I take
11 responsibility for asking the Agency to read
12 the full questions before the panel because
13 the questions are not one question, they're
14 multi-part questions with conditions said at
15 the beginning, and I wanted to make sure we
16 all saw those and were aware of it as we began
17 our discussion. Sometimes we simplify the
18 questions, but this was not a good case for
19 simplifying the questions.

20 DR. LOWIT: The Agency has
21 preliminarily concluded that atrazine directly
22 targets cells within the HPA axis, Section 3.2

1 and 3.3.2.3 of the draft issue paper -- I
2 don't know if I got all that or not -- and the
3 increased activity of the adrenal axis does
4 not reflect non-specific stress. Evidence for
5 this conclusion is based on the following
6 observations:

7 Bullet number 1, several studies
8 report increased adrenocorticotrophic hormone,
9 ACTH, and corticosterone levels immediately
10 following a single exposure to atrazine and its
11 two metabolites -- I won't say the whole
12 names -- DIA and DEA, but not DACT. This data
13 comes from the Laws, et al., Fraites, et al.,
14 and Pruett, et al., studies.

15 A single intravenous
16 administration of DEA in vivo also causes an
17 immediate increase in ACTH and adrenal hormone
18 release indicating that a chlorotriazine-
19 induced GI stress is not driving the hormonal
20 response. The adrenal corticosterone response
21 to continued oral exposure to atrazine did not
22 habituate in rats or mice. And that comes

1 from the Fraites, Laws, and Pruett papers.

2 Also, although atrazine induced a
3 rapid increase in ACTH, prolactin secretes was
4 not affected in the same animals. This is
5 unusual in that an increase in both ACTH and
6 prolactin are typically observed in response
7 to a number of physiological and psychological
8 stressors.

9 Please comment on the extent to
10 which the available evidence supports the
11 preliminary conclusion that atrazine and its
12 intermediate metabolites, DIA and DEA, induce
13 changes in the HPA axis as a result of a
14 direct action on the HPA tissue, and such
15 tissue -- such changes are not due to a
16 generalized or non-specific stress response.
17 Are there data on other substances that would
18 support this conclusion?

19 DR. PORTIER: Dr. Selvage?

20 DR. SELVAGE: Okay. That's really
21 almost a one-part question, when you think
22 about that way.

1 We can be optimistic. Let's see,
2 first I wanted to just give a preliminary
3 couple of remarks. I'm going to -- for my
4 answer I stuck to a mechanism of action. I'm
5 not really considering dose so much, because
6 the doses are obviously very, very high for
7 this.

8 Another thing I wanted to say, and
9 this is just my own personal view, is the term
10 non-specific stressor, generalized stressor.
11 You know, there's certainly stressors that
12 activate the HPA axis a number of ways, but I
13 think for each stressor, I think that there
14 are fairly specific, for instance, neuro
15 pathways, that can be activated, and can be
16 delineated with lots and lots and lots of
17 work. So I think that I'm just not a big fan
18 of the non-specific stressor. However, I do
19 realize that gets used a lot, so I just wanted
20 to say that.

21 Okay. And so then to get on to
22 the question about whether there's a direct

1 action on HPA axis tissues, once again, with
2 the HPA axis, in response to a wide variety of
3 homeostatic challenges, you know, just about
4 any homeostatic challenge you can throw, an
5 animal you can get an HPA axis response. So
6 to determine a specific action, per se, is not
7 easy, especially a specific action on HPA
8 tissues, because there could be multiple
9 actions on specific HPA tissues than actions
10 on other tissues that in turn affect the HPA
11 axis.

12 So I guess the short answer to
13 this is, you know, I don't think there's
14 enough data yet. We need more information
15 regarding atrazine's affects at a variety of
16 levels. So, and also interpretation of the
17 results presented so far is a little bit
18 difficult for me because we've got -- we're
19 using different strains of animals and
20 different species.

21 So we've got evidence in mice and
22 we've got evidence in, well, now, with Dr.

1 Handa's work, three different -- at least
2 three different strains of rats, and different
3 strains of rats all will response differently
4 to the same stressor and, you know, even the
5 vendor you get your rats from can affect how
6 they're going to respond to a stressor.

7 So it's difficult to kind of make
8 a -- you know, take all this information and
9 think that it all really, you know, fits
10 together in a cohesive manner with all these
11 different animals. On the other hand, you've
12 got a bunch of different animals and your
13 getting a similar response. So that's also a
14 positive.

15 So I guess -- let me see, once
16 again, you know, I guess it's possible with
17 the information available that the HPA
18 disruption by atrazine could be due to a
19 direct affect on HPA tissues. The evidence
20 that's been giving the supporting evidence,
21 first of all, is simply that atrazine
22 activates the HPA axis when given

1 peripherally, you know, and that's obviously
2 an important finding.

3 Also, other stressors such as
4 restrain stress, were able to cause prolactin
5 release, whereas atrazine administration did
6 not cause prolactin release, and that's given
7 as supporting evidence.

8 Also the fact that sub-
9 diaphragmatic vagotomy didn't block the HPA
10 axis response to atrazine at least rules out
11 gut irritation as the means of activating the
12 HPA axis, and then we have the information
13 that when we give, I believe it was DIA was
14 given IV, you're still able to activate the
15 HPA axis. Some other information I would say
16 would, you know, at least preliminary support,
17 looking into this hypothesis, is that atrazine
18 can get into the brain and can have affects at
19 the brain.

20 Having said that, I just think
21 there's not enough evidence to really say that
22 atrazine is acting directly at HPA tissues,

1 although you can't say it is either. And
2 with -- for instance you've got this
3 habituation of the cort response that did not
4 seem to occur, but you got -- there's
5 habituation of the ACTH response, which to me
6 makes me wonder is something going on at the
7 level of the adrenal gland, and there's some
8 information, I believe in amphibians and fish,
9 that actually -- and I believe this was
10 discounted by the EPA, probably for good
11 reason, but those two studies showed actually
12 a decrease in cort synthesis in those species.

13 So if that's actually true, the
14 you probably are working at the hypothalamic
15 level to activate the HPA axis, or, you know,
16 or some other level and not directly at the
17 adrenal gland. However, more information is
18 needed.

19 So, you know, I think there's a
20 lot of alternative hypotheses that need to be
21 investigated. The first one, which I've
22 already brought up, is I think you might have

1 an overall increase in HPA responsiveness
2 that's been to stressors in general in these
3 chronic HPA -- in these chronic atrazine
4 administration studies, which, once again,
5 brings us back to why it's important to get
6 baseline cort measurements and other time
7 points for cort.

8 Also, in the studies where we're
9 looking at chronic atrazine administration
10 over four days, or Pruett's study over 28
11 days, there were no measurements made in
12 between. And you can get alterations, you
13 know, in the HPA axis over time that we just
14 might not have seen.

15 And I think you can't really do
16 this so easily in mice, but in rats you can
17 certainly put in an IV catheter and keep it
18 patent for a decent amount of time, and you
19 could be making these measurements. So I
20 think that's something that could, and should,
21 be done. So, you know, you put in an IV
22 catheter and you indicate many draw blood

1 draws. I mean they're not going to stay
2 patent forever, but you can still do that and
3 it'd be helpful.

4 So there's also, you know, just
5 many other parameters that I think atrazine
6 could be affecting that could activate the HPA
7 axis. You know, you could get physiological
8 changes in the periphery that I don't think
9 have been examined. I did see one paper that
10 indicated atrazine actually caused
11 hypotension, a decrease in blood pressure. A
12 decrease in blood pressure activates the HPA
13 axis. I think that would need to be examined.

14 Let's see, also I think
15 sympathetic activation, activation of both
16 central catacombing noradrenergic system needs
17 to be examined more thoroughly, and also we
18 need to look at, in these animals, and you
19 could do this if you have an IV catheter in
20 place, at least -- it's a little tough, but
21 you want to look at norepinephrine and
22 norepinephrine secretion in the periphery,

1 because that can cause a lot of the affects
2 that have recorded, especially the immune
3 system affects.

4 What else do I have here. Once
5 again, I think it's important to look at more
6 central mechanisms, as Dr. Akana said, CRF,
7 vasopression, once again norephinephrine.
8 Also I think looking at the affects for PDE,
9 phosphodiesterase inhibitor, inhibition could
10 be looked at more thoroughly in the pituitary,
11 as well as in the brain because, you know, a
12 cyclic AMP, when you're increasing cyclic AMP,
13 you know, if you're doing this fairly non-
14 specifically, you could just be, you know,
15 causing a myriad of effects we haven't seen.

16 So those are my main comments
17 regarding the specific action there. You
18 know, I think other people will add a lot more
19 to this. In terms of evidence for other
20 substances, simazine was tested, which is like
21 some of the atrazine, and that had lesser, I
22 believe, activation the HPA axis, but it did

1 activate the HPA axis acutely. Was that done
2 chronically? I don't -- simazine? It was
3 just -- okay, it was acute. Okay. But it did
4 have an affect, you know.

5 Also, there's other, you know,
6 molecules like atrazine that can get into all
7 sorts of different tissues, you know. It's
8 obviously a different molecule and probably
9 will get in more tissues. But ethanol, for
10 instance, the number of way that agents like
11 that can activate the HPA axis are legion. So
12 I just think it's way too early to draw a
13 conclusion that you're directly affecting HPA
14 tissues. So give Dr. Cooper a lot more money
15 to do --

16 DR. PORTIER: Dr. Akana.

17 DR. AKANA: First off, in the HPA
18 world, if you're interested in an agent that
19 stimulates ACTH and you want to know if it's
20 non-specific, the answer is there's, in my
21 world, no such thing as non-specific stress.
22 You have uncontrolled stress, you have

1 parameters coming that you don't know about.

2 So in the HPA world, half the experiment is
3 controlling your situation to exquisite,
4 immaculate basal levels.

5 And so in both acute injection and
6 in chronic, it is really important to know you
7 have your animal in a basal condition. And in
8 many cases, that's corticosterone. Now I know
9 that's an inhibition against sampling from
10 animals if you don't have a catheter in, but
11 if you look at the literature, if you really,
12 really need to know, you can measure it in
13 urine, you can measure it in fecal boli, if
14 you really have to, which you can.

15 So I think what I can say is that
16 in response to acute injection, does atrazine
17 stimulate ACTH, I go for that. Yes, it
18 definitely does. And the more recent studies,
19 to me, are much more credible because they
20 show a wonderful control of basal ACTH and
21 corticosterone as an initial condition. And
22 that's critical in my book.

1 Let's see, on the question of
2 gastric distress, I don't think it's quite
3 definitive yet that the response to atrazine
4 is not in the gut; we have one nice vagotomy
5 experiment. But in the feeding world there's
6 an exquisitely simple experiment, is because
7 rats, and I believe mice, cannot vomit. If
8 they are given something to eat or gavage,
9 they can't get rid of it. So what they can do
10 is they run and will eat inert clay, kaolin.
11 And you can measure this. So you provide in
12 the cage a source of kaolin, and you measure
13 how much they eat. And it's very old-
14 fashioned and very simple.

15 And in the feeding world they have
16 many, many, many measures for measuring the
17 gastric distress, and a lot of them are
18 behavioral. And I think the atrazine studies
19 may be ready to look at different kinds of
20 behaviors as very sensitive indicators of what
21 kind of actions they're getting.

22 I looked in my time, I didn't see,

1 what are any affects of -- on behavior with
2 atrazine administration?

3 DR. COOPER: I'd just add one
4 quick point. Michell Hotchkiss, working in
5 Dr. Law's lab, has done the pica studies,
6 and -- right. So we have that data, it just
7 hasn't been submitted yet.

8 DR. AKANA: Oh, that will be
9 really useful.

10 DR. COOPER: And I guess without
11 giving the specifics in general, it turns out
12 that you see no change in pica behavior, no
13 increase in inert --

14 DR. AKANA: You see no change.
15 That's promising. Thank you.

16 That also reminds me that in very
17 old traditional studies with chronic stress,
18 at the end of the experiment they would
19 examine the gut for ulcers, you know, very
20 classic, very old, and very direct in this
21 particular kind of study with gavage.

22 Now when we come to the question

1 of habituation, this is a very interesting
2 nugget in this study, and it raises some
3 possibilities. First of all, in the
4 male/female difference, we'll remember that
5 females have a lot more of the binding protein
6 CBG. So this may be obscuring some of the
7 responses we see. I would love to know what
8 is the actual free corticosterone response in
9 those females.

10 And then immediately the second
11 thing is, I'm intensely interested in those
12 adrenals, and I think it's ready for studies
13 of adrenal sensitivity, both in vivo and in
14 vitro to be initiated. And that might help
15 clarify what's the male/female difference.

16 And then in my particular world,
17 when we talk about habituation and the HPA
18 system, there is one particular brain nuclei,
19 the peri-ventricular thalamus -- excuse me --
20 that's correct, the peri-ventricular thalamus
21 of the hypothalamus and I wonder if there's
22 some special susceptibility in the female.

1 And then on the concern about
2 prolactin, from -- I'm to a prolactin expert,
3 but from my review of the literature, the
4 prolactin response is not always obligate with
5 a stress response. And also, depending on
6 whether it's a predicable or non-predictable
7 stress, that's GeneQuant.

8 And also the time course can vary
9 from that which you find with corticosterone.
10 So depending on when you sample, you may miss
11 a prolactin response. There's also a diurnal
12 difference in the timing of prolactin in
13 response to, say, restrained stress. So the
14 prolactin divergence, per se, do not concern
15 me at this time. And, oh, the last point
16 which may be of interest is that the prolactin
17 response can be very dependent on the dopamine
18 total for the animal. So that's something to
19 just flag in the back of your mind.

20 DR. PORTIER: Dr. O'Byrne --
21 LeBlanc?

22 DR. O'BYRNE: I also agree, this

1 business about non-specific stress really does
2 muddy the water and should be discontinued.
3 Adding uncontrollable stress muddies it just
4 as much, in my mind. I mean people who work
5 in the stress world are plagued by sub-
6 clinical stresses, which have a nasty habit of
7 summing and synergizing and screwing up your
8 experiments. So stress is a stress, and it
9 depends on your ability to detect it.

10 In terms of the dynamics of ACTH
11 and cort release in response to atrazine seem
12 pretty normal to me. The business about the
13 ACTH not being maintained and cort being
14 maintained doesn't necessarily surprise me,
15 but from -- the HPA axis is not my baby. But
16 I do recall being confused by the literature,
17 graphs showing that ACTH doesn't always
18 increase.

19 So I think there are changes in
20 sensitivity to the -- of the adrenal level,
21 and I think this is an amazingly dynamic
22 system. So you don't necessarily always need

1 the brain to get the same degree, I think, of
2 cort response. It's a very sensible system.
3 We can switch over to a semi-automatic,
4 peripheral system, I think, in the context of
5 chronic, ongoing, or repeated stresses.

6 In term of the tools that could be
7 applied, we've got CRF1 and CRF2, not counting
8 mice. They should be used in these sorts of
9 experiments so you can get -- you know,
10 differentiate the involvement of the receptor
11 sub-types. And even if you don't want to use,
12 not counting mice -- and I have problems with
13 them, they're not as clean as people think
14 they are -- there are amazingly selective CRF1
15 and CRF2 receptor antagonists, which are
16 extremely selective, extremely potent, and
17 those are tools that should be used.

18 In the context of prolactin, I
19 don't know anything about prolactin, to be
20 honest. But it does seem a little puzzling to
21 me. But trying to do some work last night, I
22 discovered an amazing paper in 1990 -- I can't

1 remember where it was published --

2 Neuropeptides, which is, you know, a
3 reasonable journal.

4 But CGRP, given intraperitoneally
5 and subcutaneously, blocks the prolactin-
6 induced -- the stress -- that blocks the
7 progesterone increase in response to stress --
8 I can't remember what the stress was --
9 thermal stress and injection stress. And
10 that's quite interesting because I did a bit
11 of work on CGRP, which is quite potent in
12 terms of stimulating the HPA axis and
13 inhibiting the HPG axis. That's what we
14 discovered. This is calcitonin gene-related
15 peptide.

16 I mean the work didn't go any
17 further, we just beautifully described it, and
18 it fitted within the stress arena. But it was
19 quite interesting to discover this paper, that
20 it blocks the prolactin response.

21 And I think Susan's comments about
22 the dopamine system in the brain controlling

1 prolactin, there is a paper from Garla in
2 1990 -- unfortunately it's in Life Science,
3 which is a pretty awful journal, so I'm not
4 quite sure whether it'd be worth quoting --
5 but there they talk about the increases and
6 decreases in prolactin in response to
7 different stresses. So I think there's very
8 old literature on this discordance, which
9 perhaps shouldn't be of great surprise, that's
10 what I read.

11 DR. COOPER: One of the things
12 that we find consistently within the
13 hypothalamus, especially when we looked in the
14 mediobasal region when we did our
15 catecholamine work, and it's published data,
16 is that we do see the one thing that hangs in
17 there as the dose goes down is an increase in
18 dopamine, and these are, again, acute
19 exposures.

20 This is in contrast to the
21 neurotox papers that you saw that implied
22 there was dopamimetic neurotoxicity. We see

1 within the mediobasal hypothalamus an increase
2 in dopamine concentration in DOPAC, both of
3 which, of course, you know will inhibit
4 prolactin. And in our 2000 paper you saw
5 post-dependent decrease in serum prolactin in
6 estrogen-primed animals. And the other thing
7 about that is that seemed to be a brain effect
8 because of certain dynamics between how much
9 dopamine -- I'm sorry, how much prolactin was
10 present in the pituitary of those animals. So
11 what you're saying is consistent with that.

12 DR. PORTIER: Dr. LeBlanc.

13 DR. LeBLANC: I agree that there's
14 an accumulating body of evidence that would
15 indicate indeed that atrazine is affecting the
16 HPA axis in a manner that's independent of a
17 generalized stress response. But I think the
18 key word in the statement we have on the board
19 there is preliminary, preliminary conclusion
20 and I hope that's emphasized by EPA. And I
21 think we've heard that from everyone has
22 spoken, the evidence is accumulating, but as

1 there are only -- I don't think we can
2 conclude at this point that that is indeed the
3 case. We need more information.

4 And I think it's important to
5 recognize that in terms of a generalized
6 stress response, it's not driven only by ACTH,
7 and the EPA had addressed that and they've
8 looked at the prolactin response and they use
9 that as part of their evidence, and I think
10 that's good. But there are certainly other
11 hormones that should be considered.

12 And one has, thyroxine, we've
13 heard at least two studies with which
14 thyroxine levels have been evaluated, and
15 typically thyroxine levels are increased with
16 a generalized stress response. However, the
17 studies that we were exposed to, thyroxine was
18 either not affected or decreased. So, again,
19 that would argue against a generalized stress
20 response.

21 Another hormone is growth hormone.
22 It's typically decreased in stress response,

1 and I don't think anyone's looked at growth
2 hormone, but it might be something to consider
3 as additional evidence as to whether or not
4 we're looking at a generalized stress
5 response. And I think another interesting
6 aspect with respect to growth hormone, in the
7 rat at least, is that it -- growth hormone
8 regulates sex-specific cytochrome P450s in the
9 liver of the rat that could impact
10 corticosterone metabolism.

11 I'm not sure that they would
12 affect atrazine metabolism, but could affect
13 corticosterone metabolism. So it may be a
14 very -- it may provide some additional
15 linkage, or explanation that relates to the
16 sexual -- sex differences that we see in some
17 of the atrazine responses like habituation.

18 Everything else I have here I
19 think has been covered. I'm not going to be
20 repetitive. One other point, I think it's
21 important also to recognize that there could
22 be complexity here that we're not recognizing,

1 and maybe I can best explain it with an
2 example. Perhaps atrazine is indeed eliciting
3 a generalized stress response, but over and
4 above that it's impacting TSH levels, which
5 are impacting thyroxine levels.

6 And so we're saying, oh, look at
7 this profile, we're not seeing a generalized
8 stress response. But maybe we are, but in
9 addition we're seeing something else. As Dr.
10 Bucher said earlier, toxicity pathways are
11 rarely linear, typically they're webs, there
12 are many things going on. So there could be
13 additional layers here that we're really not
14 considering; we're sort of taking the easiest
15 path in trying to explain it in that manner.
16 But I think we need to recognize that there
17 could be multiple things happening. And I
18 think I'll stop there.

19 DR. PORTIER: Additional comments
20 from the panel? Dr. Selvage?

21 DR. SELVAGE: Yes, I just wanted
22 to add a couple of things. First of all, I

1 realize it's extremely easy to sit here and
2 conjecture and, you know, dream up
3 experiments, and it's much more difficult to
4 actually do them. So I want to take -- I want
5 to make sure that gets said because we could
6 probably sit here all day and come up with 10
7 years of work. But --

8 DR. PORTIER: If you didn't do
9 that, you would be a unique panel.

10 DR. SELVAGE: The other thing
11 that -- I just wanted to add one more thing
12 that might be worth looking at, but the
13 problem with having different strains of
14 animals confuses the matter a little, is that
15 it looks like with this smaller -- obviously
16 in different strains of animals, but with the
17 smaller dose of atrazine, you got, I think it
18 was 75 mgs per kg, you got at least double the
19 ACTH response in females versus 100 mgs per kg
20 in males, so.

21 And you're measuring the
22 measurements in the chronic studies, and in

1 the acute studies, the females were done on
2 proestrus at a time when, relatively speaking,
3 estradiol levels are going to be higher. So
4 they might -- that's thought to be --
5 estradiol is thought to increase HPA activity,
6 so I think it might be worth looking at
7 central sex differences as well as adrenal sex
8 differences in response -- HPA responses to
9 atrazine.

10 DR. PORTIER: Any additional
11 questions? Dr. Akana?

12 DR. AKANA: I agree that looking
13 at a stress response to atrazine is really
14 hard because you're looking at a web, an
15 ensemble of responses. So a general
16 philosophy is to look at the temporal pattern,
17 see which one changes first. And then a
18 second general strategy, which many labs do,
19 is you take down one system at a time. And
20 then if you're really clear -- for instance
21 adrenalectomy and corticosterone replacement.
22 And then if you get really bold, you do two at

1 the same time. So there are some approaches
2 that might be yielding.

3 DR. PORTIER: Anna, you had -- Dr.
4 Lowit?

5 DR. LOWIT: Yes, I was just going
6 to take the opening from Dr. Selvage to --
7 it's fascinating to sit here and listen. I'm
8 learning a lot about the stress response and
9 the HPA that I don't know if I ever really
10 wanted to know or not, but I'll soak it all
11 in.

12 Just to I guess push back a little
13 bit to -- as you're thinking about the
14 comments and writing the report, about what
15 our -- what the purpose of this is, and about
16 the value, the added value of understanding
17 every tiny detail of a mechanism when, at the
18 end of the day, the Agency needs to come up
19 with a scientifically supportable risk
20 assessment.

21 And what that means is that we're
22 going to need to derive a series of values

1 that are protective of human health. And the
2 value of -- the added value of understanding
3 every component of that web that we keep
4 hearing about in that need. So I just ask you
5 to put that in the back of your mind as you
6 make these comments.

7 DR. PORTIER: Dr. Selvage?

8 DR. SELVAGE: Yes, that's why I
9 prefaced this by saying I wasn't taking dose
10 into account, so.

11 DR. PORTIER: Dr. Reed.

12 DR. REED: Well, I was going to
13 say this to Question 1.9, but I think this is
14 a good place. I'm not going into 1.9, but I
15 think this a good place to just, you know,
16 bring out some of the endpoints. So at the
17 very tail end of this hypothesis, the
18 endpoints that we're seeing in animal studies,
19 in dogs, there's cardiopathy, there atrial
20 fibrillation in rats, and these are sort of
21 the endpoints that comes out as,
22 quote/unquote, more or less more sensitive

1 than other endpoints. Rats, extra-medullary
2 hematopoiesis in the spleen, renal effects,
3 neuropathy, just throw out some of the
4 endpoints and see if you can connect the dots
5 at the very end.

6 DR. PORTIER: Any additional
7 comments? Dr. Lowit.

8 DR. LOWIT: We don't want to get
9 into Question 1.9 here. I didn't mean to do
10 that with my comment, it's just the opening
11 was there and I felt like it needed to be
12 said. But our desire with -- the last
13 atrazine risk assessment really set a strong
14 standard by using an LH endpoint. As a
15 precursor event, we are far removed from any
16 of these more serious outcomes, and we plan to
17 follow that same approach. The ultimate
18 question is, what does that place in the
19 precursor events, to be a precursor to all
20 these other outcomes that may come up.

21 DR. PORTIER: I'm not seeing a lot
22 of additional questions, so I think we'll ask

1 EPA if they got out of this what they were
2 looking for.

3 I mean, you know, my take on this
4 is that they don't like this non-specific
5 stress term and they really kind of have
6 explored -- like you said, they've explored
7 the stress question quite a bit trying to put
8 your experiments in a --

9 DR. COOPER: If I could just make
10 one comment, final comment. Yes, I think
11 these have been extremely helpful. I think
12 that some of the directions that have been
13 suggested this morning are already being
14 pursued. We're one lab, three PIs, and we
15 published the first paper on the adrenal
16 access in November or December, I forget
17 exactly when it came out. So this is
18 relatively new to us. We're not experts in
19 HPA by any means.

20 The connection was there in the
21 literature. We continue to be confused by the
22 acute versus chronic outcomes, and the onus is

1 on us, and I think others, to looking into the
2 connections, if they are there. We can't
3 ignore them. They're big flags that at least
4 in the endocrine world are important to us.
5 So all this has been helpful.

6 The suggestions about knock out
7 specific receptor blockers for CRF,
8 measurements of CRF, AVP, these things are
9 hitched into. And I have one technician, and
10 these ladies behind me have one each too, so
11 if we had the world enough and time enough, we
12 may have been able to address those things.
13 But this is useful.

14 And we see this as not our
15 research, per se, it's a research area that
16 there's a lot of very well-qualified labs
17 around. It's an extremely interesting series
18 of events that occur, and the more we can
19 enlist the basic scientists in these kinds of
20 questions, the happier we are.

21 One other thing about dose, I
22 think we constantly are dealing with the

1 issues of dose and route of administration of
2 those kinds of things. They're not foreign to
3 us, but sometimes the restraints of the
4 question put us -- so we're looking at little
5 parts of the bigger picture and you see these,
6 and of course those are all very good comments
7 that we've received about that, and we
8 appreciate them.

9 DR. PORTIER: Let's take a break
10 until 10:30.

11 (Whereupon, the above-entitled
12 mater went off the record at 10:14 a.m. and
13 resumed at 10:33 a.m.)

14 DR. PORTIER: So, Dr. Lowit, I was
15 trying to summarize Question 1.3 and kind of
16 looking over my notes, and I get the feeling
17 that Dr. LeBlanc's comments were probably the
18 most pertinent ones in saying there's an
19 accumulating body of evidence, but it's
20 preliminary and there's need for more
21 information.

22 And we got a lot of suggestions of

1 where the additional data, addition
2 information will come from. And I've talked
3 to the panel members, and the -- kind of the
4 details on that additional information that
5 they'd like to see and the stress-related
6 impacts, that that's all going to be put in
7 the report.

8 And I do think there's a general
9 acknowledgment of what EPA's trying to
10 accomplish with this in terms of their need
11 for a risk assessment. And you're going to
12 see some of that. It may extend then to
13 academic research needs, but there's -- I
14 think there's a good recognition of where you
15 need to go with this.

16 DR. LOWIT: I think some of these
17 issue will -- what I'll call the collision
18 between the risk assessment world and the
19 academic world will probably reappear in
20 Question 1.9, so I think I'll hold back sort
21 of pushing any more around that, because the
22 question is when is enough enough.

1 DR. PORTIER: And I'm making kind
2 of a list of issues as they come up here
3 that'll come back up again in 1.9 where we
4 starting looking at issues like acute versus
5 chronic definition, how do we look at that,
6 and health effects and how do we define those
7 health effects. And so we'll just kind of
8 keep track of those and that'll be our catch-
9 all question.

10 So with that we're going to move
11 on to Question 1.4.

12 DR. LOWIT: We threw together a
13 quick slide to sort of do the -- but we have
14 to either switch the video thing, or get it to
15 John's computer. It's on my machine.

16 DR. PORTIER: That's okay. It'll
17 just a second.

18 (Pause.)

19 DR. PORTIER: Now we took a break
20 and everybody distressed and got their cort
21 levels low, now don't -- you know, don't raise
22 it just yet.

1 DR. LOWIT: Except Nelson and I,
2 because we've been sitting here doing this.

3 Okay. So this is not what Dr.
4 Pastoor showed, you know, thinking where are
5 those little box and whisker plots and where
6 are the margins of difference. Intentionally
7 not there. We, as a team, as an agency across
8 three offices, came into this meeting focused
9 entirely on science, and focused entirely on
10 a lot of very difficult science that may or
11 may not have a lot of impact on what is
12 already a very complicated risk assessment.

13 And so you may, after seeing Dr.
14 Pastoor slide, notice there's a vast crevasse
15 where our documents to you don't talk about
16 this stuff, and that's, in many ways,
17 intentionally. We want this meeting to be
18 about science and to be about the science that
19 informs our decisions, not necessarily about
20 the decisions that we haven't made and haven't
21 figured out how to make yet. That's why
22 you're here to help us, guide -- to guide us

1 to make the right ones.

2 So you haven't heard us talk about
3 points of departure, except for I think two
4 bullets in Liz's slide yesterday. We haven't
5 talked about uncertainty factors, we haven't
6 talked about margins of exposure, we haven't
7 talked about RfDs, we haven't talked about any
8 of that because we want this to be about
9 science and it's very complicated all by
10 itself.

11 And when you bring in a lot of
12 very complicated policy on top of the science,
13 it gets confused. And so we want this meeting
14 to be about science and about the science that
15 will help us to go in different directions to
16 inform the decisions that we have to make.

17 So what we're getting back to is
18 not what you -- I don't think what you've
19 asked for, but I think it's what you really
20 need.

21 And that may be a little
22 patronizing on my part. I apologize for that.

1 Oh, piddle. That came out in not the right
2 way. I'm sorry about that.

3 Oh, well, it's too late now, it's
4 on the record. And my slide just went away.

5 So what is worth taking a minute
6 to talk about is what it is that we need.
7 Okay. We, at the end for the day -- what
8 happened to the computer?

9 DR. PORTIER: I think when you
10 close it, it --

11 (Pause.)

12 DR. LOWIT: Okay. Don't touch.

13 DR. PORTIER: Don't stress.

14 DR. LOWIT: Don't stress. Right.
15 I'll check my cort levels.

16 This would be acute or chronic, I
17 don't know. It was atrazine, it's both I
18 guess. What we need at the end of the day is
19 science had informed some difficult decisions,
20 and one of the most important ones we have to
21 make this choice about is what we call the
22 point of departure. And what that is is a

1 value that we'll select, or a series of values
2 for that matter, that represent whether it's
3 a NOEL or LOEL or a benchmark dose, hopefully
4 for precursor event and mode of action for
5 atrazine that represents a level by which we
6 can -- act as a starting point to create a
7 risk assessment that's safe for human health.

8 And those can get very
9 complicated, especially for something like
10 this, because duration is an issue, and we've
11 heard a lot about acute versus chronic, and I
12 think the grayness between acute and chronic
13 I think is probably more important to us
14 than -- as much as anything right this second
15 because we need a -- we will need a certain
16 amount of clarity around the relationship
17 between the HPA and HPG and the clarity of
18 those key events to get a handle on how often
19 we need to monitor and water. So whether it's
20 days or weeks or months or years, that kind of
21 resolution is important to us.

22 Life stage is also important,

1 whether it's adults, it's pregnant females,
2 it's newborns, it's in utero, it's postnatal,
3 it's perinatal, it's pubertal for lack of a --
4 it's a route. We look at point of departure
5 by route. I think for atrazine route is less
6 important because we're really in this
7 analysis looking at oral exposure and drinking
8 water. But for a lot of other assessments we
9 think about things in other routes.

10 The other pieces that we need will
11 be, since we'll be determining a point of
12 departure from animal data, we'll have to
13 extrapolate from animals to humans and that's
14 how you will go from one of those steps that
15 Dr. Pastoor talked about, one of those orders
16 of magnitude to go from the animal value down
17 to a human equivalent value. There are
18 different ways of doing that. The standard
19 way is to divide by 10. There are more
20 sophisticated approaches it can be upon.

21 From that point we go what we
22 think of as the average human to a sensitive

1 human, and standard procedure will be to
2 divide by another 10. There are also most
3 sophisticated ways of doing that, that could
4 be anything from something smaller to
5 something far larger.

6 Specific to the Pesticides Office,
7 since we work under the Food Quality
8 Protection Act, Congress mandates that we add
9 a 10X factor for the protection of infants and
10 kids, and that value is only removed with
11 sufficient data on hazard and exposure.

12 And so the default window of
13 uncertainties is 1,000. It can be bigger or
14 it can smaller depending on the situation,
15 depending on what science informs the animal
16 to human, the human sensitivity, or the FQPA.
17 So you may start with a default of 1,000,
18 bigger or smaller, depending on the science.

19 Drinking water, Dr. Pastoor had a
20 series of box and whisker plots, and I believe
21 there quite a bit of comments from Dr. Young
22 wondering about the differences in the --

1 looking at the totality of the data set versus
2 individual sites. And I think our message
3 tomorrow will be very clear that we assess
4 risk to individuals at individual sites
5 because every site has its own atrazine level
6 and we have to make sure that the people in
7 those sites are protected as individuals.

8 DR. THURMAN: And this is Nelson
9 Thurman. Just to give you an idea of how we
10 do the drinking water component part of it,
11 because we know we have to -- the temporal and
12 spatial variability we talked to you about, we
13 have to account for that. We know we're not
14 going to get coverage everywhere, over all
15 dates.

16 So what we end up doing is
17 focusing on what we think are the most
18 vulnerable areas, or the most vulnerable
19 systems. A lot of times that's done based on
20 something like a WARP model, something like --
21 based on our best information we have based on
22 the relative -- on the crops being grown, the

1 relative vulnerability of the sites, the
2 weather patterns. Sometimes in the case of
3 atrazine, it's based on the fact that we do
4 have Safe Drinking Water Act monitoring over
5 time that tells us -- helps us zoom in on
6 where we think the most vulnerable systems are
7 going to be.

8 The goal is, if we can protect
9 those systems, we're protecting the less
10 vulnerable systems. We don't go into this
11 saying that all systems are in trouble. We
12 know that there -- that we're zooming in on
13 the most vulnerable, and the idea is that's a
14 sensitive sup-population for us, and so we
15 want to make sure that we're safe on that
16 level.

17 We also need to account for that
18 temporal variability over time. And we need
19 to be able to match that to the hazard
20 assessment. So that's what we try to do. A
21 lot of cases we use deterministic models
22 because that's the one we have. In the case

1 of atrazine we do have a wealth of monitoring
2 data. With that sampling, as I pointed out
3 yesterday, even interpreting monitoring data
4 is a model.

5 And so we need to account for what
6 kind of uncertainty do we get in those
7 sampling frequencies so that we make sure that
8 we're not saying, This is safe, whenever the
9 actual exposures would be greater. That's our
10 biggest concern in that regard, so, and that's
11 why the questions we have before you on
12 drinking water, the intent is for you to help
13 us figure how best to quantify that
14 uncertainty in sampling frequencies and how we
15 deal with if that duration exposure changes so
16 that we can then go back and determine on
17 those individual systems are they safe or do
18 we have things we need to do.

19 DR. LOWIT: Okay. So just to sort
20 of close this out, and how those -- how all
21 these pieces are matched, it gets very tedious
22 and complicated very quickly, particularly as

1 you think about multiple durations and
2 multiple life stages and many different CWSs,
3 of different levels all over the country
4 that -- how those values will be matched.

5 That you'll match the points of
6 departure from the appropriate duration from
7 the most sensitive life stage, to the -- from
8 the right routes, to individuals that match
9 those profiles in that drinking water area.
10 So if it's an infant, you'll match it an
11 infant water consumption; if it's a adult, you
12 match it to the adult consumption, and that's
13 done for every individual CWS. And as Nelson
14 mentioned, across the country the amount of
15 atrazine in the water varies greatly.

16 So to try to bullet what those
17 values and those margins of exposure are in
18 three bullets is -- doesn't necessarily
19 provide the fullness and the robustness of
20 what the risk picture looks like, because it
21 varies a great deal across the country.

22 Oh, and the last point is that

1 it's less important to think about those
2 margins of exposure for the 2003 risk
3 assessment because we've gone into this
4 analysis with a clean slate. That's the last
5 risk assessment. We're going into this with
6 a clean slate to ensure that everyone around
7 the country is protected.

8 DR. WILLIAMS: I think -- yes,
9 that was pretty much what I needed, not what
10 I asked for. The only question I have is how
11 do you -- back to Dr. O'Bryne's question --
12 that the very low doses that were going down
13 from these what seem to be considered kind of
14 high-dose treatments of rats and so forth, how
15 do we know that these low-dose exposures
16 themselves do not have long term chronic
17 effect. Has that been looked at, is it being
18 looked at, or is that just out of the realm of
19 this handle and shouldn't be considered?

20 DR. LOWIT: Well, to the extent
21 there is -- there are chronic long term rat
22 studies, and certainly the mammary tumors were

1 a topic that Syngenta covered quite a bit
2 yesterday, so there is -- there are a series
3 of chronic studies in rats. There is the
4 standard, what we'll call the guideline set of
5 different kinds of toxicities, developmental,
6 reproto, cancer, different durations, that sort
7 of thing.

8 There is also what we're -- one of
9 the things that we will do in the September
10 meeting is to bring in the epidemiology from
11 the human epidemiology literature that has its
12 own challenges. But we'll provide a more full
13 picture of the totality of the toxicity
14 profile I think.

15 DR. PORTIER: Dr. Young?

16 DR. YOUNG: Given the nature of
17 these sites and the fact that they're likely
18 to be spread out, does it -- spatial
19 correlation, and I know the emphasis here is
20 temporal, but isn't one of the reasons is the
21 sites are likely so far apart that spatial
22 correlation is questionable?

1 DR. THURMAN: Yes. You know,
2 that's a question -- it depends on what scale
3 you're looking at, but, yes, I think that
4 spatial correlation on a localized scale is
5 going to be very questionable. I think in
6 general we can identify areas where there's a
7 higher likelihood of high exposures, and
8 that's something we've learned a lot more
9 about as a result of the eco-monitoring that
10 I think we're just starting to say these are
11 things we can start at those. But more of
12 a -- in classic geospatial sense, that
13 correlation is not as -- it's not going to be
14 easy to find, if it exists.

15 DR. YOUNG: Yes, because the
16 higher levels are likely a change of mean and
17 not necessarily reflective of a correlation
18 structure once they get that far apart.

19 DR. PORTIER: Thank you very much.
20 I think we need to move on to
21 Question 1.4.

22 DR. LOWIT: Dr. Cooper can read.

1 DR. COOPER: This must be another
2 bad question.

3 DR. PORTIER: And actually it
4 doesn't even look like a question, it's just
5 please comment.

6 DR. COOPER: Yes. Charge Question
7 1.4, based on a review of in vitro studies
8 evaluating the effects of atrazine on estrogen
9 production, the Agency has preliminarily
10 concluded that atrazine does not have a direct
11 effect on the catalytic activity of aromatase.
12 However, with continued exposure, atrazine can
13 cause increased estrone and estradiol
14 production the H295R and JEG-3 cell lines,
15 Sanderson, et al., 2000; Laville 2006; Higley,
16 et al., 2010.

17 These changes in estrogen
18 production have been associated with increased
19 cyclic AMP, and CYP19, and message RNA,
20 Sanderson, et al., 2000, 2001, that are part
21 of a complex mode of action through which
22 atrazine up-regulates the gene expression of

1 aromatase and possibly other enzymes within
2 the steroidogenic pathway, Section 3.3.2.3 and
3 Figure 3, Arrow 7 on the draft issue paper.
4 Wow.

5 The hypothesis that atrazine
6 alters multiple steroids is supported by the
7 increased testosterone concentrations in H295R
8 cells following exposure to atrazine, Higley,
9 et al., 2010, and in vitro studies
10 demonstrating that atrazine affects a number
11 of signal transduction pathways and/or
12 transcription factors in a variety of cells
13 Suzawa and Ingraham 2008; Albanito, et al.,
14 2008.

15 Up-regulation of the expression of
16 a group of major steroidogenic genes has been
17 observed in JEG-3 cells, Susaw and Ingraham,
18 2008. In vivo, there is little evidence that
19 atrazine alters aromatase, per se, Modic 2004,
20 and the evidence associating atrazine exposure
21 to increases in serum estrogens appears to be
22 related to a general increase in gonadal and

1 adrenal progesterone and androstenedione,
2 Modic 2004; Laws 2009.

3 Where is the question mark?

4 Please comment on the extent that
5 the available data do or do not support the
6 Agency's preliminary conclusion that atrazine
7 has a general stimulatory effect on
8 steroidogenesis, as opposed to a direct effect
9 on aromatase.

10 DR. PORTIER: Dr. LeBlanc, your
11 comments.

12 DR. LeBLANC: Thank you.

13 I really don't like reading
14 verbatim to an audience, but I have a lot of
15 factual information here, so I am going to
16 read, and please bear with me. But the enzyme
17 aromatase is a product of the CYP19 gene and
18 it's responsible for the aromatization of
19 androgenic C19 steroids to estrogens, 17-beta-
20 estradiol, estrone, et cetera.

21 Aromatase is expressed in various
22 tissues in both males and females. Gonadal

1 expression of aromatase is largely responsible
2 for elevated plasma levels of estradiol and
3 related estrogenic hormones in reproductively
4 mature females. Aromatase is also expressed
5 in other tissues, however, including bone,
6 brain, placenta, and others, in males,
7 immature animals. In reproductively senescent
8 females, plasma estrogen levels were likely
9 the product of aromatase activity in these
10 other tissues.

11 Aromatase gene expression in these
12 different tissues is under different
13 regulatory controls. The tissue-specific
14 regulation stems from the existence of
15 multiple promoter regions on the gene, the
16 CYP19 gene, that control the expression and
17 the differential production of estrogens in
18 response to different stimulatory factors,
19 hormones, et cetera.

20 In the ovary, aromatase is under
21 the regulatory control of gonadotropin
22 follicle stimulating hormone, FSH. FSH is

1 produced by the pituitary gland, it stimulates
2 a signal transduction cascade within the
3 ovary, the granulosa cells, resulting in
4 intra-cellular elevation of cyclic AMP levels.
5 The elevated cyclic AMP levels then stimulate
6 the association of the transcription factors
7 SF1 and CREB to their adjacent response
8 elements resulting in stimulation of the CYP19
9 gene expression.

10 So in this situation we have two
11 adjacent response elements and there are two
12 factors that are involved, SF1 and CREB. CREB
13 is phosphorylated and apparently both of these
14 transcription factors need to bind, and in
15 doing so then recruit other players that
16 stimulate transcription of the aromatase gene.

17 Adipose aromatase appears to be
18 under the joint regulatory control of
19 cytokines, including TNF-alpha, IL-6, IL-11,
20 it's under the influence of glucocorticoid
21 hormones, as well as the transcription factor
22 SP1. So there are multiple players in

1 regulating the expression of aromatase in the
2 adipose tissue. The cytokines stimulate
3 transduction pathways within the adipose sites
4 that result in the interaction of the
5 transcription factor STAT3 and possibly others
6 with their response elements.

7 Glucocorticoid hormones will bind
8 to their glucocorticoid receptors and bind --
9 this complex then binds to the glucocorticoid
10 response element to regulate gene
11 transcription. The glucocorticoid receptor --
12 I'm sorry, SP1, which is activated by a
13 phosphorylation event, also binds to a
14 response element within the motor region of
15 CYP gene to regulate gene transcription.

16 Together these transcriptional
17 regulators stimulate aromatase activity in the
18 adipose tissue, and, again, these factors
19 don't seem to function independently in
20 regulating transcription, but seem to
21 cooperate in the regulation of transcription
22 in adipose tissue. Thus, chemicals that

1 modulate any of these pathways could
2 potentially impact aromatase expression.

3 Finally, in the placenta,
4 aromatase appears again to be under multiple
5 regulatory controls, and there's much less
6 known about the regulation of aromatase in the
7 placenta, but perhaps most relevant to our
8 discussions is that ligands to the retinoid X
9 receptor, RXR, appear to be involved. And
10 accordingly, compounds such as retinoids,
11 fatty acids, as well as some xenobiotics could
12 influence aromatase activity via this
13 regulatory pathway.

14 Now we know that atrazine has been
15 shown to elevate aromatase activity in
16 cultured cells, and at issue here is whether
17 or not this is a specific affect of atrazine
18 on aromatase, or some generalized affect on
19 steroidogenesis. In terms of atrazine
20 directly impacting the catalytic activity of
21 the aromatase enzyme, I'm aware of no
22 precedent for this in the literature. I'm

1 furthermore not familiar with any precedent of
2 the aromatase enzyme being susceptible to
3 allosteric interactions, et cetera, that would
4 result in some direct increase in catalytic
5 activity through interacting with a ligand.

6 As discussed above, there are
7 multiple regulatory elements through which
8 atrazine could impact the expression of the
9 CYP19 gene, and the greatest evidence that
10 exists is interaction involving the cyclic AMP
11 SF1 pathway. Atrazine has been shown to
12 increase cyclic AMP levels in cells, and it
13 has also been shown to activate SF1 via
14 increased phosphorylation.

15 There is one paper that indicates
16 that atrazine actually binds to SF1 and
17 activates, but that's been discounted in at
18 least one other paper, and I think the
19 argument against that is rather good. So I
20 don't argue that SF1 may be activated, but I
21 don't think it's through direct interaction
22 with the atrazine. I think it's through

perhaps a phosphorylation event.

Now, at it turns out, SF1 is not a -- the signaling pathway is not a specific regulatory process for aromatase. SF1 is recognized as generally stimulating steroidogenesis in cells, and so it may very well be that this effect of atrazine on the SF1 signaling pathway is indeed a general effect on the steroidogenic pathway and not specifically on aromatase. And I say that with caution because I'm not trying to imply that it's a non-specific effect. It is a specific effect but involves multiple player in steroidogenesis.

So the conclusion can be made that atrazine's effects on aromatase gene expression represents a generalized effect on steroidogenesis, probably mediated by SF1 and cyclic AMP. Potential interactions of atrazine via other known regulatory sites, however, must be evaluated. There are a lot of potential regulatory pathways through which

1 atrazine could be acting, and they haven't
2 received a lot of attention. And I think we
3 need to consider that.

4 For example, the glucocorticoid
5 hormone pathway. It has been evaluated with
6 respect to whether or not atrazine binds to
7 glucocorticoid receptor, and the evidence
8 indicates that it doesn't. However, we do
9 know that atrazine stimulates glucocorticoid
10 levels, so in that respect we could be
11 inducing endogenous glucocorticoid levels with
12 atrazine treatment that is resulting in a
13 stimulation of aromatase via the
14 glucocorticoid hormone pathway that can't be
15 excluded at this point.

16 SP1 was another transcription
17 factor involved, and I could find no evidence
18 that atrazine has an effect on SP1. The
19 information simply isn't out there to make a
20 judgment one way or another. The same thing
21 for RXR. I identified RXR as a potential
22 target for atrazine, but at this point in

1 time, as best that I can determine, there's no
2 evidence to indicate whether or not atrazine
3 is binding and activating the RXR.

4 So in conclusion, there's
5 significant evidence that atrazine has the
6 potential to regular gonadal CYP19 expression
7 through the stimulation of the cyclic AMP SF1
8 signaling pathway. This effect would be
9 expected to be common to most sterogenic
10 pathways along the hypothalamic, pituitary,
11 adrenal, or gonadal axis. It functions on
12 both axes.

13 It's also plausible that atrazine
14 stimulates adipose CYP19 expression through
15 its activation of the HPA axis resulting from
16 the increased glucocorticoid levels that we
17 see with atrazine treatment. And that's all.

18 DR. PORTIER: Thank you.

19 Associate discussant Dr. Delclos.

20 DR. DELCLOS: I won't have that
21 much to say. I think that, as indicated in
22 the document, as Dr. LeBlanc has said, there's

1 clear evidence that the ATR do not directly
2 interact with aromatase, but that the enzyme
3 is induced after longer term exposure in
4 several cell lines in vitro. And one thing
5 that struck me in reading the literature, and
6 was pointed out in the public comments
7 yesterday in the Syngenta, is that most of
8 these in vitro studies take -- do not take
9 into account the metabolism and the
10 relationship of -- they use atrazine, they
11 don't take into the account the metabolic
12 capabilities of the -- in the animal and what
13 happens and it seems like the metabolites are
14 really the major players after atrazine gets
15 in the body.

16 But that being said, there are a
17 couple of studies that did use the metabolites
18 and they found that the major metabolite,
19 DACT, is not active, but the two
20 monodealkylated metabolites, DIA and DEA, are
21 active, although they may be a little less
22 potent than ATR itself. So there is some

1 relevance of these in vitro activation studies
2 perhaps.

3 But there is little evidence in
4 the rodent studies, or there's no direct
5 evidence in the rodent studies that aromatase
6 is being elevated in vivo. The only evidence
7 that's been used to support that is the
8 pattern of hormone stimulation and reduction
9 in the testosterone elevation of estradiol and
10 estrone. The studies that have directly
11 looked at aromatase elevation, the Modic
12 thesis that was presented, and the rest, and
13 the Sanderson abstract, showed no evidence
14 that gonadal aromatase is induced in vivo
15 after atrazine exposure.

16 Several possible other
17 explanations for the elevation of estradiol
18 and estrone have been presented, including
19 increase for the aromatizable androgenic
20 substrates effects on metabolism of the
21 estradiol, or induction of adipose aromatase,
22 and I think that hasn't been worked out.

1 But there is some evidence from
2 the in vitro studies, the study by Higley that
3 was cited, that there is a general activation.
4 And as Dr. LeBlanc talked -- said, there are
5 multiple pathways that have been proposed to
6 be affected by atrazine or its metabolites
7 that may support a general induction of
8 steroid synthesis.

9 So I think that there is no -- to
10 summarize, there is no existing evidence in
11 the rodent studies that there's an elevation
12 in vivo, and there is supporting evidence that
13 there's a general increase in steroidogenesis,
14 so I think the hypothesis is supported,
15 although it's not definitively proven; there's
16 still work to be done in that regard.

17 DR. PORTIER: Thank you.

18 Dr. Horton?

19 DR. HORTON: Thank you.

20 Just a reminder that when you're
21 talking about steroidogenesis in vivo, and
22 particularly when you're talking about the

1 ovary and testes, you're talking about a very
2 complex organ. Steroidogenesis in the ovary
3 is a two-cell process that requires the
4 interaction between the fecal and granulosis
5 cell, and you have to have enzymes in two
6 different cells working together. You also
7 require the interaction between two
8 gonadotropin in order to make the ovary work
9 properly, and those two gonadotropin must be
10 secreted in sequence in order to have the
11 ovary work properly in its cyclic fashion.

12 And what I've not heard discussed
13 is the role of atrazine or any impact of
14 atrazine on the secretion of follicle
15 stimulating hormone. I've heard a great deal
16 of discussion of the role of atrazine on the
17 secretion of luteinizing hormone. So what's
18 missing from this discussion is the potential
19 impact of the set up of the ovary and its
20 preparation for steroidogenesis by follicle
21 stimulating hormone, because in an ovary that
22 is not prepared properly, it will not respond

1 to luteinizing hormone in the appropriate way.

2 So I would encourage any studies
3 to -- in the future to also examine the levels
4 of follicle stimulating hormone. Thank you.

5 DR. PORTIER: Dr. Williams.

6 DR. COOPER: Can I just make one
7 comment?

8 DR. PORTIER: Sure.

9 DR. COOPER: FSH has been looked
10 at in the ovariectomized estrogen primed
11 female and in the male, and there hasn't been
12 really any change noted in that they're
13 relatively short term treatments. That's just
14 the background that somehow slipped. I
15 apologize you didn't see that.

16 DR. PORTIER: That was Dr. Cooper,
17 EPA.

18 Dr. Williams?

19 DR. WILLIAMS: I would say I don't
20 have anything to add to what's already come
21 out. I agree with the comments that have been
22 made.

1 DR. PORTIER: Dr. Schlenk?

2 DR. SCHLENK: Yes. One of the
3 things we've dealt with a lot with -- in terms
4 of pesticide metabolism, is that with drug
5 interactions, oftentimes when you see issues
6 related to clearance, it's not necessarily
7 induction of pathways, it's actually
8 inhibition of pathways. They tend to be more
9 thermodynamically sort of, you know, favored,
10 if you will.

11 One of the things I didn't see in
12 the White Paper, and has not been mentioned
13 all that much, are the inhibition of catabolic
14 pathways that atrazine may actually take --
15 have some impairment on. And I know I think
16 we talked earlier, CYP3A is actually inhibited
17 fairly potently by atrazine, at least in about
18 a one to two micromolar, and I've got a
19 reference to throw in the report.

20 But one could argue that the
21 enhancement of the steroid levels perhaps
22 would be due to inhibition of catabolism

1 perhaps, of steroid -- rather than looking at
2 the steroidogenic pathway, but actually
3 looking at the catabolic pathway that actually
4 keeps the levels high. And honestly,
5 thermodynamically that would make a little bit
6 more sense perhaps. But it may be, again, a
7 minor pathway outside of what the hormonal --
8 luteinizing hormone issue is related to that.
9 Just something to consider.

10 DR. PORTIER: Additional comments?

11 (No response.)

12 DR. PORTIER: I won't even attempt
13 to summarize this. I'm assuming Dr. LeBlanc's
14 got it all down and, well, his comments were
15 pretty clear, if you could follow it. Which
16 I'm sure Dr. Cooper could; maybe not the rest
17 of us.

18 I think the general conclusion was
19 that -- let's see if I can -- clear evidence
20 it's not direct. That's what I got out of
21 this. There's a lot of evidence for indirect,
22 but not a lot of evidence for direct effects.

1 Okay. Why don't we move on to
2 Question 1.5 then.

3 DR. COOPER: Charge Question 1.5,
4 a series of studies evaluating the effect of
5 either peripubertal or gestational exposure to
6 atrazine in the male rat indicate that
7 atrazine decreases testosterone concentrations
8 and may lower androgen dependent tissue
9 weights, but that it has little effect on
10 basal LH secretion in the male. This response
11 generally occurs at doses of 50 milligrams per
12 kilogram and above.

13 In contrast, atrazine in vitro has
14 been found to consistently increase steroid
15 hormone production. Thus, there is an
16 apparent discrepancy between the in vivo and
17 in vitro data. However, our understanding of
18 the interplay between the adrenal and the
19 gonadal axis may provide an explanation --
20 period. An explanation.

21 (Laughter.)

22 DR. COOPER: At the doses used in

1 the in vivo studies, atrazine induces an
2 activation of the adrenal axis, increased ACTH
3 and corticosterone, and the increase in
4 corticosterone does not habituate, i.e. it
5 does not lessen with repeated dosing. There
6 are a number of studies in the literature
7 demonstrating that prolonged corticosterone
8 stimulation will impair testosterone
9 production by a direct action on
10 steroidogenesis in Leydig cells.

11 Therefore, in vivo effects of
12 testosterone synthesis are likely the result
13 of an adrenal hormone-mediated down-regulation
14 of the HPG axis through corticotropin
15 releasing hormone, CRH modulation, or GnRH
16 pulsatility, or directly in the testes through
17 a glucocorticoid receptor-mediated change in
18 steroidogenesis.

19 Please comment on the degree to
20 which the proposed mode of action, Figure 3 of
21 the draft issue paper, provides a biologically
22 plausible explanation for the decrease in

1 serum testicular testosterone identified in
2 the in vivo studies. Please comment on the
3 extent that the available data do or do not
4 support this hypothesis.

5 DR. PORTIER: Dr. Delclos is the
6 lead discussant.

7 DR. DELCLOS: Okay. Well, the
8 white paper reviews several studies in which
9 testosterone levels are replaced by exposure
10 to atrazine during the peripubertal or
11 gestational period, and at least one study
12 where exposure to commercial formulation
13 involving atrazine in inerts in adults reduced
14 testosterone, and there was generally no
15 consistent corresponding effect on LH,
16 although there was evidence of a decreasing
17 trend in at least one study, the Stoker study.

18 There was no direct assessment of
19 the HPA axis in these studies, but the
20 proposed MOA involving HPA axis is certainly
21 plausible, given the known suppressive effect
22 of corticosterone and corticosterol -- or

1 cortisol on the HPG axis at all levels, and
2 the clear evidence that, from other studies,
3 that atrazine can stimulate the HPA axis at
4 levels at which the testosterone reduction has
5 been reported. So there is suggestive
6 evidence supporting this MOA.

7 But there are a few issues. As I
8 said on the first day in my question, I'm
9 intrigued by this fact that the major
10 metabolite, DACT, affects puberty, which is a
11 sensitive short term endpoint, but does not
12 affect, or only weakly affects, the HPA axis.
13 And the pubertal delay can occur at levels
14 below those at which ACH, cortisol increase,
15 the corticosterone increases have been
16 demonstrated. Presumably this affect on the
17 HPG axis is important in this delay in the --
18 in puberty in the males.

19 And at least in the one -- in the
20 study of the male, the PK study by Ross, which
21 is the only one that I'm aware of that looked
22 at specific metabolites in various tissues,

1 but they did find high persistent levels of
2 DACT in the brain. So I think this is just
3 something that could be -- should be further
4 evaluated.

5 The other issue was the Rosenberg
6 study which indicated that prenatal exposure
7 led to a lasting affect on testosterone and
8 delayed preputial separation, and there was no
9 data on the HPA axis provided from that
10 exposure, but where expected activation in the
11 dam was likely.

12 I'm not really too aware of the
13 effects of activation of HPA axis on puberty.
14 I know that there's at least one study looking
15 at I think dexamethasone to the dam indicating
16 that puberty can be delayed, and there was a
17 paper last year from Richard Sharp's lab in
18 which he was -- looked at the affect of
19 dexamethasone on dibutyl -- interaction with
20 dibutyl phthalate in reduction of
21 testosterone, and he had indicated that there
22 was no effect of dexamethasone on the --

1 directly on the testosterone levels. There
2 was a decreased birth weight in the
3 neonatal -- in the pups, but that it greatly
4 enhanced the ability of dibutyl phthalate to
5 reduce testosterone synthesis.

6 So, again, this is -- these are
7 just the, as I say, the proposed mode of
8 action is plausible, but I think it needs to
9 be further evaluated in these -- particularly
10 in the pubertal exposures and the gestational
11 exposure.

12 DR. PORTIER: Dr. LeBlanc?

13 DR. LeBLANC: Ample evidence
14 indicates that atrazine stimulates the
15 hypothalamic-pituitary-adrenal axis resulting
16 in increased production of adrenal
17 corticosteroids and progesterone. Induction
18 of HPA axis is well known to suppress the HPG
19 axis predominantly through the inhibition of
20 hypothalamic GnRH and/or the secretion of
21 gonadotropin inhibiting hormone resulting in
22 the suppression of LH from the pituitary.

1 And I find this proposed mechanism
2 for the suppressive action of atrazine on
3 testosterone production largely plausible.
4 There are issues that I still struggle with,
5 and I'll try and communicate right now. One
6 is that -- well, we had this issue of
7 discrepancy between in vitro and in vivo
8 observations, and it seems to me that the
9 weight of the evidence is indicating that in
10 vitro we're looking at the perturbation of the
11 axis, and that's perfectly plausible.

12 And it appears that in vitro we're
13 seeing effects, at least on aromatase, via
14 some direct regulatory pathway within the
15 cells. And right now SF1, cyclic AMP seems to
16 be the -- there's the most evidence for and
17 interaction at that level. However, and so
18 the presumption would be that both of these
19 processes would take place in vivo, but I
20 suppose the effects on the axes perhaps
21 predominate and so we're not seeing the
22 induction of aromatase in vivo, or it might be

1 a consequence of pharmacokinetics of atrazine.

2 I certainly don't know the answer to that.

3 However, the pituitary also is
4 regulated by SF signaling, specifically LH
5 production -- SF1 signaling. I'm sorry. And
6 so if we accept the premise that SF1 is having
7 a stimulatory affect, it certainly raises
8 issues as to why we're not seeing a
9 stimulatory effect of the activation of SF1 at
10 the level for the pituitary, which would
11 result in an enhanced steroidogenesis. I'm
12 not sure.

13 The other thing I struggle with is
14 if we're looking at an overall -- let me think
15 about this. I'm going to stop there. I'm
16 going to get myself too deep into a hole here
17 that I'm not going to be able to get out of --

18 (Laughter.)

19 DR. LeBLANC -- and I don't think
20 I'll contribute anything of significance. So
21 I'll stop there.

22 DR. PORTIER: Dr. O'Byrne.

1 DR. O'BYRNE: I just have one
2 comment to make. In the context of decreasing
3 luteinizing hormone, I see it time and time
4 again, it's difficult to see a reduction in
5 gonadal intact animals. That doesn't mean to
6 say there isn't a decrease because it's below
7 the detection of the assay, and that is
8 something that really has to be taken on
9 board. So when people say there's no
10 decrease, I don't believe it. And that's all.

11 DR. PORTIER: Dr. Selvage?

12 DR. SELVAGE: From what I've
13 heard, I don't think I can really add much
14 more to this. So I will pass.

15 DR. PORTIER: Dr. Williams.

16 DR. WILLIAMS: The only thing I
17 would add is the -- in thinking about kind of
18 peripubertal or gestational exposures, what
19 really hasn't come out -- we've talked about
20 direct effects, but thinking about kind of
21 epigenetic changes that are going to later
22 impact on many different systems.

1 So, you know, the cell culture
2 evidence I think it's pretty straightforward
3 and easier to interpret. But the in vivo data
4 I think is going to take a lot of mechanistic
5 examination before we can really clearly put
6 a story together, which I think is what Dr.
7 LeBlanc was getting at. But it's going to be
8 really complicated. And if you, you know,
9 directly answer the questions here, you know,
10 there's a general stimulatory effect. I mean
11 that seems rather superficial when you
12 consider what might really be going on from a
13 neuroendocrine standpoint.

14 DR. PORTIER: Additional comments
15 from the panel?

16 (No response.)

17 DR. PORTIER: So what I read from
18 this is that the -- the mechanism of action is
19 plausible, all right, but really needs more --
20 at least the in vivo is plausible but needs
21 more explanation, and the in vitro stuff is
22 what it is. I mean you believe the in vitro

1 stuff, but the in vivo, more mechanistic
2 information to really be able to interpret why
3 it tends to conflict. Is that a clear
4 summary?

5 (No response.)

6 DR. PORTIER: Additional comments?

7 (No response.)

8 DR. PORTIER: I'm not sure that
9 helps, but --

10 (Laughter.)

11 DR. PORTIER: I want to give Dr.
12 LeBlanc a few more minutes to think through
13 this. I can just see the wheels turning.
14 He's thinking, Well, maybe I'll get this
15 figured out by lunch.

16 I don't think we're going to get
17 much more from the panel on this.

18 Dr. Lowit?

19 DR. LOWIT: Even with the lack of
20 clarity I think we heard what we were looking
21 for.

22 DR. PORTIER: Dr. LeBlanc.

1 DR. LeBLANC: Just one comment. I
2 think one of the reasons, at least one of the
3 reasons that I struggle with this, and I'm not
4 as close to the data as Dr. Cooper is, but it
5 seems to me, with respect to steroid hormone
6 levels, depending upon which study you're
7 looking at, different things happen.
8 Sometimes things go up, sometimes things go
9 down, sometimes they don't change. And so,
10 you know, I don't think we can explain that
11 right now, but it's also hard to come up with
12 a biologically plausible explanation for
13 what's going on.

14 I mean, does the weight of the
15 data indicate that testosterone is going down?

16 DR. COOPER: There's several
17 different studies and several different dosing
18 regimens, but as the background paragraph said
19 in this thing -- it did a good job of
20 capturing that anyway, I think -- is that the
21 studies that have been done generally imply
22 there's a decrease in T, but they're, you

1 know, they're in vivo, longer dosing, and
2 that's that disconnect between the in vitro
3 and the in vivo studies.

4 I will add that there is evidence
5 that there's an increase in testosterone in
6 Leydig cell preparations. And that was
7 done -- increase in testosterone production --

8 DR. LeBLANC: In the cells but not
9 in the plasma?

10 DR. COOPER: In vitro, the --

11 DR. LeBLANC: Oh, in vitro.

12 DR. COOPER -- in purified Leydig
13 cell preparation, which is another -- those
14 studies were done as a part of the EPA's
15 Endocrine Disruptance Screening Testing
16 Program's development of the H295R cells,
17 whereas background work that was done in
18 those -- this isn't published, so we couldn't
19 lay it out there, but I think for
20 clarification the studies that have been done,
21 they were comparing directly Leydig cells
22 against H295R to see how representative the

1 295R were of the "real thing," rat Leydig
2 cells.

3 And the data that has been
4 obtained so far -- and, again, these are
5 different labs that ran these studies --
6 showed that -- and they were looking at the
7 production of testosterone and estradiol --
8 that not only did estradiol or estrone,
9 whichever your measurement -- your
10 estrogen you wanted to measure, were increased
11 in response to atrazine. Again, going back to
12 the Sanderson work and one of the primary
13 reasons they selected that cell line, but also
14 the testosterone increased.

15 And the Higley paper points to
16 that H295R data, and as a part of the
17 supporting validation of that assay, the
18 Leydig cells were compared, and in the Leydig
19 cells they saw increased T. That's the in
20 vitro evidence that it's increased
21 steroidogenesis more than just estradiol, and
22 in addition other hormones were looked at and

1 they were up.

2 And then there's this acute
3 increase in testosterone that you'll almost
4 always see when you look in vivo, but the
5 chronic it's always decreased, and that's
6 what's the disconnect that we were seeking
7 guidance on, which we probably confused you
8 more than we're confused.

9 DR. PORTIER: I don't think we saw
10 any additional insight. That's -- if I
11 could -- if I heard that.

12 Any additional comments?

13 (No response.)

14 DR. PORTIER: I'm going to leave
15 this question open because I really do see the
16 wheels turning. I suspect he'll come back
17 from lunch with a light bulb over his head.

18 Why don't we -- we're going to
19 move on to the next question, 1.6. I don't
20 think we'll finish it before we break for
21 lunch, but we can begin the discussion on that
22 question. And it may take us 15 minutes just

1 to read the question.

2 DR. LOWIT: We're going to do a
3 quick musical chairs.

4 DR. PORTIER: Bringing in the
5 neurotox expert. Right?

6 DR. LICCIONE: I was hoping Ralph
7 Cooper would read this because he's had a lot
8 of practice today, but I'll try to read slow,
9 I'm not as experienced as he is.

10 Based on a review of the
11 neurotoxicity studies, Section 3.4 of the
12 draft issue paper, the Agency has
13 preliminarily concluded that several recent
14 studies provided further support for the
15 concern that dopaminergic neurotransmission
16 may be affected by atrazine, a concern that
17 was raised by studies prior to 2003.

18 However, the Agency has concluded
19 that several aspects of these studies of the
20 dopaminergic neuronal pathways, in particular
21 the changes noted in the stereological
22 evaluations and the observed changes in

1 behavior, should be considered as preliminary
2 findings. And in my presentation I also
3 emphasize inconclusive.

4 This conclusion is based on the
5 notable limitations identified in the data
6 including, one, a lack of clear dose-response
7 relationships; two, lack of inclusion of
8 suitable positive controls to confirm the
9 competency and reliability of the procedures
10 utilized in examining dopaminergic systems in
11 the brain; three, limited data to corroborate
12 stereological findings; four, limited or no
13 supporting histological and behavioral
14 assessments; and, five, no consideration of
15 the potential role of the HPA axis, for
16 example, alterations in corticosterone.

17 EPA has further determined that
18 two non-dompaminergic neurotoxicity studies,
19 one on brain somatostatinergic systems and the
20 other on neurobehavior in mice, also have
21 significant limitations. For example, the
22 lack of details on the source and purity of

1 atrazine; the age and body weights of the
2 mice; poor quality of the amino cupric silver
3 staining photomicrographs; limited
4 presentation of the reverse-transcriptase
5 polymerase chain results; lack of data to
6 corroborate the conclusion of neuronal
7 degeneration; reference citations did not
8 support statements made in the text; no
9 explanation of biological plausibility of the
10 alterations in somatostatinergic receptor sub-
11 types; inappropriate statistical evaluation of
12 data, litter versus the pup; discrepancies in
13 the number of pups examined for behavioral
14 endpoints; and lack of objective and validated
15 behavioral tests. Please comment on these
16 preliminary conclusions regarding the
17 neurotoxicity findings.

18 Okay. The Agency has
19 preliminarily concluded that the available
20 studies indicate that the neurotoxicity
21 endpoints examined are not more sensitive than
22 those evaluated for neuroendocrine function

1 following atrazine exposure. For example,
2 attenuation of the LH surge and estrous cycle
3 disruptions in female Sprague-Dawley rats
4 which form the basis for the current chronic
5 RfD.

6 In addition, the Agency has
7 concluded that there is no association between
8 atrazine exposure and development of
9 Parkinson's disease on the basis of non-
10 specificity of effects on brain dopaminergic
11 system, lack of histological and behavioral
12 features characteristic of Parkinson's
13 disease, and results of epidemiological
14 studies. Please comment on this preliminary
15 conclusion.

16 DR. PORTIER: Thank you.

17 So, Dr. Horton, it looks like we
18 have two comments we're looking for. And turn
19 on your mike, please.

20 DR. HORTON: Let's see if I
21 managed to respond to both of those. Okay.
22 In response to the first comment, the Agency

1 provides information in Section 3.4 of the
2 white paper and the presentation given on
3 Monday, that there reason for concern that
4 dopaminergic transmission may be affected by
5 atrazine, as shown by studies conducted prior
6 to 2003. The Agency then reviews two more
7 recent studies, Belloni, et al., and Coban and
8 Filipov 2007, which provide additional data
9 reaching similar conclusions.

10 In addition to previous
11 suggestions that atrazine may negatively
12 impact dopamine transmission, the Coban and
13 Filipov study also suggests that serotonergic
14 systems may be involved. Additional studies
15 were presented suggesting that atrazine may
16 also influence somatostatinergic systems as
17 well as other neuropeptides. Any alteration
18 in these neural pathways may ramify through
19 many homeostatic, neurobehavioral, and
20 metabolic systems, as mentioned in the
21 response to Question 1.2.

22 Although each study individually

1 suffers from technical errors and problems
2 with reporting and should be considered
3 preliminary as is consistent with your
4 conclusions -- or the conclusions of the
5 Agency, when considered in total, the emerging
6 body of evidence suggest an area of concern
7 that requires further investigation into the
8 neurotoxicity and neuroendocrine effects of
9 atrazine across all stages of a life span in
10 environmentally relevant doses.

11 These areas of concern include the
12 prenatal/perinatal periods and effects in
13 adulthood on a wide range of neurotransmitter
14 systems should also include the oft neglected,
15 but nevertheless important glia, and bring
16 regions other than those defined by a strictly
17 Parkinson's disease model. Research should be
18 conducted with consideration to the fact that
19 there are critical periods during development,
20 both prenatal and postnatal, including during
21 the adolescent period -- see work by Cheryl
22 Sisk and others, and I'll provide a list of

1 references -- when transient exposure to
2 chemicals can have permanent organizational
3 effects on the nervous system.

4 Additionally, cumulative exposures
5 to steroids and/or stress is proposed to have
6 cumulative or allostatic affects on health,
7 and I can provide references. There's a
8 recent reference that has just appeared in the
9 general Hormones and Behavior by Bruce McEwan
10 and John Wingfield. That has just appeared in
11 Hormones and Behavior 2010.

12 Of concern to human health and
13 well-being is the suggestion that atrazine may
14 affect numerous regions and neurotransmitter
15 systems. Careful wording must be used when
16 reporting these new developments. Use of the
17 phrase non-specific, as with a non-specific or
18 non-Parkinsonian model, conveys a sense of
19 unimportance. In contrast, the possibility
20 that multiple neurotransmitter systems are
21 involved, in fact, should shift our focus on
22 the mode of action.

1 The early studies were focused on
2 a model fo Parkinson's Disease. The realities
3 of current research funding mechanisms often
4 force researchers to squeeze their work into
5 the context of one disease model or another,
6 whether the square peg fits in the round hole
7 or not. With the emergence of more research,
8 the peg may not fit, and appears not to fit
9 the Parkinson's disease model, but now needs
10 a new hole of its own.

11 The emerging preliminary data do
12 suggest a plausible link and basis for
13 additional studies related to the new mode of
14 action for atrazine proposed in the Agency's
15 white paper. Additional research is needed to
16 determine the size and shape of the new peg
17 and the new hole, including studies
18 specifically designed to evaluate the changes
19 in neurotransmitter and neuropeptide systems
20 in -- concerned in the context of the broader
21 mechanism of action proposed in the white
22 paper.

1 For the record, researchers
2 working with animals face increasing
3 limitations on their ability to meet the
4 criteria set forth by the EPA for determining
5 whether data are acceptable. Researchers are
6 under increasing pressure to limit the number
7 of animals used in their work, and one
8 question they must respond to on every animal
9 care and use regulatory form is whether or not
10 an experiment replicates an experiment
11 conducted by their laboratory or any other
12 laboratory or any published study.

13 It is increasingly difficult to
14 get permission to replicate a study that has
15 been done in the past, and to get permission
16 to conduct that study from your institutional
17 review board. Any attempt to replicate
18 results -- or any attempt to replicate results
19 of a previous study must be done in the
20 context of new studies, thereby increasing the
21 complexity of an experiment, thereby often
22 weakening your statistical power.

1 We encourage the EPA to
2 communicate with the National Institutes of
3 Health, the Department of Agriculture, the
4 National Science Foundation, and the American
5 Association for Laboratory Animal Care, the
6 accreditation agency for animal facilities, to
7 the extent possible to make them aware of the
8 EPA's guidelines for acceptable data. Thank
9 you.

10 DR. PORTIER: Thank you.

11 Dr. Chambers.

12 DR. CHAMBERS: Thanks.

13 I think points are well taken, but
14 I think I'm going to take a different tack on
15 answering this question. I think a number of
16 people around the table today have mentioned
17 the dose levels that have been used in a lot
18 of these studies, and I'd just like to
19 reiterate my concern about some of those dose
20 levels too.

21 Necessarily, in academic labs I
22 think we need to go to high doses just to sort

1 of justify that we get some results that we
2 can publish, but that doesn't necessarily do
3 you a whole lot of good in the regulatory
4 arena, and I'd like to emphasize that.

5 Another point along those lines
6 too, is when you start using these
7 astronomical doses that we've seen numerous
8 times in these studies, you pretty much
9 obliterate the metabolism in other sorts of
10 defense mechanisms, and so they're not
11 necessarily realistic. So the mode of action
12 you discover at those high doses may not be
13 anywhere near reality.

14 With respect to your first
15 question there, I think -- I looked at all
16 those studies and I concur with the
17 deficiencies that you identified, and so I
18 don't see that many of them are very useful
19 for risk assessment. They certainly are not
20 designed and not done to the quality that you
21 expect out of the registrants and the other
22 types of studies that are used in the

1 regulatory sense.

2 Just for, I guess, the sake of
3 transparency, I do want to mention that the
4 Filipov studies, and there are three of them,
5 did come out of a center grant that I was in
6 charge of at the time. I did not collaborate
7 on those studies; I had nothing to do with
8 them. As a matter of fact, I did comment on
9 the high doses and did object to those at the
10 time, but they got done anyway. But at any
11 rate, I don't -- I thought maybe I better say
12 that just in case anybody knows where Filipov
13 was at the time that he did those studies.

14 So you identified a number of
15 rather non-specific effects -- oh, I shouldn't
16 use non-specific I guess -- sort of scattered
17 effects, non-dose responses, scattered types
18 of things, and I don't think they really
19 reflect a strong indication of neurotoxicity.
20 Probably the study that is most useful from
21 the standpoint of identifying whether any of
22 these neurotoxic mechanisms on dopamine are

1 any more relevant to your point of departure
2 in risk assessment would be the Rodriguez
3 study, and I still have difficulty with the
4 way they tried to describe dose levels there.

5 And, Ruby, I tried to interpret
6 that the way you did yesterday, too, but I
7 looked again last night, and every time where
8 they talk about the chronic dose levels in the
9 feed, they just say five mgs per kg or ten mgs
10 per kg and don't identify day. And I see in
11 your write-up you identified day, and that's
12 sort of the interpretation. But nevertheless,
13 that is not the way you express chronic doses,
14 and so it was really very difficult to tell
15 what they were being exposed to.

16 They should have described, for
17 something like that, a feeding study, was this
18 put in pellets, was this powdered form, and,
19 you know, did the animals scatter it and did
20 they really understand how they were getting
21 it, is it something they put on cookies, like
22 sometimes we do with feeding studies and so

1 forth? And so I think you're really left with
2 not knowing for sure how they animals were
3 dosed and how consistent that five or ten mgs
4 per kg per day, I presume, was done.

5 I'm concerned -- so that probably
6 is some of the lowest dose data that's in this
7 mix. I'm rather concerned about the
8 stereological results because those have a
9 tremendous amount of overlap in the individual
10 animals between the treated and the control.
11 So I'm not really convinced that there's an
12 effect there. There was a limited number of
13 animals that are presented and the -- again,
14 a tremendous overlap between the controls and
15 treated. So if there's anything there, I
16 really do think that needs some sort of repeat
17 some time along the line.

18 I'm not sure what else to comment
19 on that except, again, these are not data that
20 are consistent enough and well-described
21 enough for you to conclude anything other than
22 that they are preliminary and they have

1 limitations.

2 With respect to the Parkinson's
3 disease question, I think the studies that
4 have implicated Parkinson's disease there are
5 basically an over-interpretation of the
6 results that they've gotten. I'm not
7 convinced that the studies that they've done,
8 because of the behavioral endpoints and that
9 sort of thing, are really suggestive of an
10 implication in Parkinson's disease. That's
11 not to say that that isn't true, but there's
12 nothing in these studies, I think, that really
13 suggests that.

14 So I am in concurrence with your
15 evaluation of those papers that they are
16 preliminary, they're non-conclusive, and they
17 probably do not lead to any suggestion that
18 these effects should supplant the POD that
19 you've already got in place.

20 DR. PORTIER: Dr. Reed.

21 DR. REED: First of all, I want to
22 thank the Agency for putting all the

1 literature paper and its collections in such
2 an organized fashion. It really helped to go
3 in -- you know, the summary, the review
4 they're very helpful to guide me in terms of
5 which particular article that I want to zoom
6 in. I did go and get all the articles, so
7 that helps too. And so that, you know -- what
8 I mean is that we don't have to agree with the
9 review or the interpretation of this study,
10 but the guide is great.

11 Let me see, for the first
12 question, again, my take is going to be
13 slightly different, so that's great. You
14 know, all three of us look at different
15 aspects of the issue. So I also agree that
16 the Agency came to the preliminary conclusion
17 about the findings being preliminary because
18 of limitations.

19 Basically, when I look at
20 neurotoxicity, I am looking at whether CNS,
21 PNS have been affected, and atrogen
22 technically is neurotoxic. I think what was

1 puzzling and what all the studies were going
2 about is trying to connect between mode of
3 action and the manifestation of that, which we
4 are not clear about how many different mode of
5 action or networks involved, and so it's sort
6 of at this stage impossible to connect to the
7 two. And we're going to be seeing a lot of
8 that expression within, you know, our meeting
9 here.

10 I have one comment because I came
11 to the same conclusions as Dr. Chambers that
12 if I were to look at the endpoints, which
13 would have some kind of an impact on risk
14 assessment, it will be the Rodriguez study
15 because of the low, you know, NOEL. And I'm
16 not trying to defame the study at all because
17 I'm not entirely clear about how the dose was
18 decided, I just caught on the fact that it
19 says that they controlled the diet, so I
20 figured that they must have made measurements
21 of the diet in order to control the body
22 weight.

1 I am impressed with the fact that
2 these are fairly recent studies, and so, you
3 know, yesterday I mentioned with the
4 oncogenicity part of our discussion and in my
5 questions, you know, during the presentation,
6 and also I'm just struck by the fact that if
7 something is important, can we perhaps make an
8 effort to contact the author and maybe clarify
9 some of these points? I mean if we think
10 there is value in it, I would encourage the
11 Agency to do that.

12 I notice that one of the authors
13 in the Rodriguez study is actually from the
14 Agency. Am I correct on that? Maybe I
15 wasn't. But -- is it? Okay. Well, in any
16 case, that's what I'm thinking, that if it is
17 possible to contact the office, we might be
18 able to get information if dose is the issue.

19 DR. LICCIONE: I have a comment
20 though about the confidence in the study. I
21 mean I think at face value, as Dr. Chambers
22 mentioned, the stereological results, I have

1 zero confidence in that. And I have a number
2 of problems with the behavioral assessments.

3 DR. REED: Right. Right.

4 DR. LICCIONE: I believe that in
5 contacting them we would have to address a lot
6 of these limitations --

7 DR. REED: Right. Right.

8 DR. LICCIONE -- rather -- in
9 addition to clarifying the dosing regimen,
10 which I also had difficulty understanding
11 because they didn't provide the correct
12 information.

13 DR. REED: Right. No, no, I
14 wasn't --

15 DR. LICCIONE: But I think --

16 DR. PORTIER: That was Dr. Luebke.

17 Dr. Reed?

18 DR. LOWIT: Luccione.

19 DR. PORTIER: Luccione. He got it
20 wrong.

21 Dr. Lowit.

22 Okay. Back to Dr. Reed.

1 DR. REED: No, no, I totally agree
2 with you. I just haven't done with the
3 concept. I'm saying that if it is just a
4 matter of dose, then, you know, we can go and
5 contact, but I think there's some protocol
6 observational issues that we might not be able
7 to resolve is what I was going to say. So
8 that's good. We're all in agreement with each
9 other.

10 In terms of neurotoxicity, I ask
11 myself what kind of an endpoint am I looking
12 for anyway, and it's going to come up in
13 Question 1.9, but what I'm thinking of, and,
14 you know, it's something sort of -- focused me
15 in the sync, it was because I notice that some
16 of the studies, they might not be listed
17 within this group, actually came up with
18 clinical sign kind of effects, and I don't
19 know the reasons behind it, but I think that
20 that might be something, you know, worth
21 looking into in terms of manifestation of
22 neurotoxicity.

1 Let me see. I think I would focus
2 on neurobehavioral and neurodevelopmental,
3 which my understanding is that we don't have
4 something like that. I don't want to be the
5 R2D2 type of person as a risk assessor, but it
6 might be worthwhile for the Agency to, instead
7 of saying that we don't have enough
8 information, these are all preliminary, we
9 don't think the endpoint is going to be more
10 sensitive than what we've been looking at,
11 since we haven't defined that so we cannot
12 make such conclusion, it might be worthwhile
13 to look into the possibility of -- and I think
14 the Agency accumulated a lot of great
15 information, asking a lot of good questions
16 about neurotoxicity, that it might be possible
17 to work together in coming up with a
18 neurodevelopmental study, or even FOB type of
19 study, at least explore that possibility. I
20 think it's good to well characterize it before
21 we throw it away saying it's not as sensitive.

22 DR. CHAMBERS: Let me ask a

1 question since this is a pesticide, was a DNT
2 study conducted on it? No?

3 DR. LOWIT: No, there's no DNT.

4 DR. PORTIER: What does that stand
5 for?

6 DR. LOWIT: Developmental --

7 DR. CHAMBERS: Developmental
8 neurotoxicity study.

9 DR. LOWIT: Sorry.

10 DR. CHAMBERS: Sorry.

11 DR. REED: Can I make a comment or
12 question? I don't think there's FOB study.
13 Right? Was there?

14 DR. MENDEZ: I don't believe so,
15 but I'm not 100 percent sure --

16 DR. REED: Acute versus chronic
17 or --

18 DR. MENDEZ: I don't think that we
19 have an acute neurotoxicity study, if that's
20 what you're asking.

21 DR. REED: And so these are the
22 two, DNT and the neurotoxicity studies is what

1 I'm referring to.

2 DR. LOWIT: I guess I'll go back
3 to one of my comments earlier about the --
4 particularly the DNT that costs somewhere in
5 the order of 7, 800, up to, you know, upwards
6 of a million dollar study, and many, many,
7 many animals. The value added of that study,
8 given the nature of the totality of the --
9 what is known about atrazine and that we're
10 really diving down into more precursor events,
11 and DNTs, developmental -- you know, the
12 stuff, the alphabet soup -- developmental
13 neurotoxicity studies are not always the most
14 sensitive studies, and it's, at least my
15 personal opinion, it's highly unlikely that
16 study would give you anything lower than the
17 things that we're talking about for the --
18 related to the hormones.

19 DR. PORTIER: Dr. O'Byrne?

20 DR. O'BYRNE: My understanding is
21 that atrazine has been around for 60 years.
22 Surely there's some clear epidemiology -- epi

1 data because some of these male farmers must
2 be now in their 80s. So is there not a clear
3 guidance from that sort of data, clinical epi
4 data on Parkinson's?

5 DR. LOWIT: I missed the first
6 half of the question. You're asking about --

7 DR. O'BYRNE: It's been around for
8 60 years. Farmers have been spraying it on
9 their crops. And some of those guys now must
10 be in their 80s, so is there is any epi data
11 showing that there's an increased incidence of
12 Parkinson's disease? Do we need animal
13 models?

14 DR. LOWIT: There is -- our
15 epidemiological evaluation is still ongoing,
16 but there is -- atrazine was included as part
17 of the Agricultural Health Study, and there is
18 a relatively recent study on Parkinson's, and
19 atrazine was not one of the pesticides where
20 they saw a positive statistical association
21 with Parkinson's in pesticide applicators.

22 DR. PORTIER: Was it Dr. Horton?

1 Yes. And then Dr. Chambers.

2 DR. HORTON: One of the things I
3 want to make sure that we made clear is the
4 distinction between neurotoxicity and
5 neurodevelopmental effects. Whereas, you
6 know, we have one killing neurons in an acute
7 fashion, whereas exposure at different stages
8 of life altering a developmental program, and
9 I think those are two very different things
10 that have to be examined, which is why, in my
11 statement, I commented that the studies need
12 to be examining factors at different life
13 stages.

14 And I think that is some of what
15 needs to be examined in terms of looking at
16 weight of the evidence. And I think looking
17 at the totality of the evidence, regardless of
18 what you're looking at in terms of the doses
19 and things here, there is some suggestive
20 evidence that points in that direction.

21 The other question I have is for
22 Dr. Liccione -- okay. I'll get it. When you

1 say you discount the stereological data, part
2 of it was you commented on the calibration.
3 Could you comment -- or explain why you
4 discounted it and which specific study?

5 DR. LICCIONE: Okay. The
6 Rodriguez in particular --

7 DR. HORTON: Okay.

8 DR. LICCIONE -- the stereological
9 showed, as Dr. Chambers said, when you see the
10 overlay from a variability, the stereological
11 results should account for a coefficient of
12 error biological variation to give you a
13 handle of the statistical dispersion. Because
14 stereology is based on random systematic
15 statistical sampling, which is often used in
16 survey sampling, and one has to address those
17 statistical issues in looking at it because
18 stereology has not gained wide acceptance yet
19 because of a lot of problems with methodology
20 and statistical error.

21 DR. CHAMBERS: This is Janet
22 Chambers. I just wanted to make sure that my

1 question wasn't interpreted as a suggestion
2 that DNT be run. I was just thinking that
3 perhaps it was already part of your data sets.

4 But I think sort of following onto
5 that conversation that was going a few minutes
6 ago, I think what you all really need to do is
7 make sure that you're looking at what appears
8 to be most sensitive out there, and not
9 requiring a lot of data that are just probably
10 going to be false leads because they're only
11 go to show effects at higher levels and all.

12 You've got the data sets that you
13 can look at for the most sensitive effects.
14 I think you pretty much decided that the
15 neuroendocrine appears to be the most
16 sensitive effect right now, and going into a
17 bunch of other types of data requirements or
18 data studies that are not related to the very
19 sensitive effects are probably not going to
20 lead to anything very useful.

21 DR. PORTIER: My understanding of
22 the question to the panel though is whether

1 you think the neurobehavioral, neurotox
2 effects are less sensitive than the endocrine.

3 DR. CHAMBERS: And I think I'll
4 try to answer that again, Ken. Based on these
5 particular papers that we saw, I don't see
6 that they are -- there is anything that is
7 more sensitive than the other endpoints that
8 they've used up till -- that you've used up
9 till now.

10 DR. PORTIER: But I think we have
11 some -- actually, I think Dr. Reed was next,
12 and then Dr. Horton.

13 DR. REED: By saying
14 neurodevelopmental effects, I also don't mean
15 the standard -- what I said is that the Agency
16 had gathered a lot of information by now
17 specific to atrazine, but I thought by working
18 together you might be able to come up with a
19 valid -- a study to study the
20 neurodevelopmental effect manifested from --
21 whether it's, you know, endocrine effects or
22 not, because I think you're going to get a lot

1 of questions further down the road about what
2 happened to the pre- and post -- prenatal and
3 perinatal exposures, and how is that
4 manifested in -- during the development. That
5 was what I -- I didn't mean the standard DNT
6 study either.

7 I'll let Dr. Horton comment, and
8 then I'll come back to the next one.

9 DR. HORTON: Okay. In that
10 context I think all three of us are in
11 agreement in terms of, you know, at the
12 current state of development of the data, the
13 answer to the second question of are the
14 neurotoxicity data more sensitive than the
15 endocrine data. No, because the data are
16 simply not good enough. They're, you know,
17 they're clearly preliminary. That is
18 absolutely clear. They're very preliminary.

19 What the data suggests is that
20 there is a possible mode of action and a
21 plausible reason to suspect that there is
22 something going on that is consistent with the

1 suggested mode of action that has been
2 discussed in context of the other question
3 that is worth additional investigation.

4 DR. PORTIER: Dr. Reed.

5 DR. REED: Okay. So my second
6 part of comment is this, that the endpoint for
7 neuroendocrine aspect has not been clearly
8 defined. I mean it's a mode of action, it's
9 not an endpoint, and when it comes to endpoint
10 for risk assessment, I'm not quite sure yet
11 how that line is going to be drawn in terms of
12 what is the manifestation of that and, you
13 know, and so forth.

14 So given that the information
15 right now is available, they don't look "more
16 sensitive," but that, again, is just looking
17 at the mode of action, not the dose response
18 and not the result of the cascade of events
19 that would come out at the very end in terms
20 of the endpoint. I feel like it's premature
21 for me to say that the neurological endpoints,
22 including the neurodevelopmental and all the

1 other, you know, endpoints put together, is
2 less sensitive.

3 I think that's probably a little
4 bit different -- you know, less sensitive than
5 the neuroendocrine type of endpoint, because
6 if we're looking at either the same or similar
7 mode of action or a different mode of action,
8 we haven't even defined what that endpoint is.
9 So we're saying there's not enough
10 information, you know, from the neurotoxicity
11 part of the database, it's not the same as
12 saying because we don't have that, so it's not
13 going to be more sensitive. Does that make
14 sense?

15 DR. HORTON: I would say this is a
16 case where there's a difference in the
17 statement the data don't support versus there
18 are no data. And in this case the statement
19 is there are no data, not the data don't
20 support. And so it's a need for more data.

21 DR. PORTIER: That was Dr. Horton.

22 That's exactly what I was trying

1 to get. The point is I don't think they're
2 answering your question about which one's
3 better, and they're basically saying, we don't
4 have enough data on the neurotoxin,
5 neurobehavioral endpoints to be able to make
6 that assessment. And Dr. Reed is leaving open
7 the issue that a neurobehavioral endpoint may
8 actually be the key health effect that they
9 may be looking at.

10 DR. REED: Which we don't know at
11 this point.

12 DR. PORTIER: Dr. Chambers.

13 DR. CHAMBERS: But I don't think
14 these data sets are suggestive enough to say
15 that you really need to launch a big effort to
16 look for that at this point. I mean there's
17 a little bit of stuff that's low dose in what
18 we looked at, and it really is not showing a
19 good dose response curve on the neurochemistry
20 or the behavior or any of the endpoints that
21 were looked at in stereology, any of that, to
22 suggest that this is -- this has really got a

1 lot of plausibility in terms of displacing
2 what you already know in terms of the most
3 sensitive effect. If I'm getting the sense of
4 what you're asking.

5 DR. PORTIER: I was going to make
6 a suggestion that we leave this question open,
7 take a break, come back right after lunch and
8 continue, kind of -- because I feel like we're
9 kind of going in a little bit of a circle
10 here, no data, can't decide, not enough data
11 to decide if we need to suggest even more
12 research. So we're kind of caught in a loop
13 here.

14 So let's break till 1:15. We'll
15 reconvene at 1:15.

16 (Whereupon, the above-entitled
17 matter went off the record at 12:04 p.m. and
18 resumed at 1:16 p.m.)
19
20
21
22

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:16 p.m.

DR. PORTIER: Before we get started, we need to kind of close off Question 1.5, and I just wanted to look over at Dr. LeBlanc and see if he'd had a brainstorm over lunch and whether he wanted to revisit it. If not, we'll close it off.

DR. LeBLANC: Well, I can say that in the hour I had during lunch, I thought about it definitively, I've worked out the mode of action, all the intricacies --

(Laughter.)

DR. LeBLANC -- but for the sake of staying on schedule, I won't speak.

DR. PORTIER: It'll be in the report. Okay. So I'll assume that Question 1.5 is closed now. But I just wanted to leave that open just in case.

And we still have before us Question 1.6. And my reason for leaving it open is still trying to get to this second

1 comment question, which is the more
2 sensitive -- are the neurotoxicity endpoints
3 examined are more sensitive than those
4 elevated for neuroendocrine function. And I
5 realize that there's lack of data and the two
6 studies that we looked at, or the studies that
7 we've looked at, have serious limitations.

8 But the question -- I think the
9 question behind the question here from EPA is
10 is this something they need to go and continue
11 to get data on because it is likely to be more
12 sensitive, or is it something they need to go
13 get data on because it'll round out the issue,
14 or is it not something they need to go get
15 data on. I guess those are the three -- yes,
16 Dr. Horton.

17 DR. HORTON: Okay. So you gave me
18 a multiple-choice question. I think the
19 answer to your question is B. And if B was
20 that there -- no, it's not to just round it
21 out, but it may -- getting more data -- no,
22 it's actually all of the above, which wasn't

1 on your list.

2 The choices were, because the
3 data -- the current data are insufficient to
4 give us an answer to anything, if we have more
5 data will it just round out our understanding
6 of the mechanism of action of atrazine, will
7 the provision of more data give us a better
8 understanding of a more sensitive endpoint,
9 and will it tell us whether there's a more
10 sensitive endpoint.

11 And all of those things are true
12 because it is possible and more relevant here
13 to your regulatory and risk assessment, it's
14 possible that if there are developmental
15 effects, that those could be assessed at an
16 earlier stage and recognized at an earlier
17 point in an experiment and be more focused and
18 with greater, shall we say, gain in an assay
19 system, making for greater statistical power.
20 If you're looking at -- particularly if you
21 could put them into a neurobehavioral context
22 where you can do multiple studies or multiple

1 measurements on an animal in a behavioral
2 screen.

3 As have been done by many of the
4 NIH cores that are doing behavioral screening
5 cores for the neurogenomics screens, the
6 mutagenesis screens where they're looking for
7 point mutations in response to chemical
8 mutagens, and they have batteries of
9 behavioral endpoint, circadian rhythms
10 endpoints, whole panels of neurobehavioral
11 tests that they put the same animals through
12 at different developmental stages, and we do
13 this at Northwestern in our neurobehavioral
14 core, of Rotarod tests and grip tests and the
15 same animal will be put through 15 different
16 types of tests to screen them for various
17 anomalies.

18 And so you could put them through
19 essentially a high-output screening test to
20 look for a variety of things. And so if you
21 can set up a screening program for that, you
22 might be able to pick up a behavioral anomaly

1 on the same animal at a fairly efficient cost
2 and with a great deal of power.

3 DR. PORTIER: So, but what's the
4 expectation that that effect is going to occur
5 at a dose, say, lower than an endocrine
6 impact? And so that's one part of it. The
7 other part of it is the difference between
8 objective and subjective measurements. Right?
9 And a lot of the neurobehavioral stuff is
10 relatively subjective.

11 I know they're improving the
12 methodology, but a lot of it, you know, you
13 need many more animals -- they're not
14 sacrificed, that's good -- many more animals
15 to come up with that good definitive finding
16 of a small behavioral change. At least the
17 stuff that I've seen in the years we've been
18 before here, whereas a lot of people like the
19 objective measurements. Now you did mention
20 some, you know, like genomic screens and
21 stuff, those are more objective measures.
22 Right? The kind of repeatability is pretty

1 high.

2 DR. HORTON: Well, I would say the
3 kind of behavioral testing that I'm thinking
4 of are things like circadian rhythms where
5 you've got the animals on a running wheel, and
6 I would counter by saying some of the weakness
7 in the endocrine studies is that unless you're
8 doing pulsatile bleeding for some of these
9 endocrine measures, you're going to miss
10 changes. And that is very labor intensive for
11 what you're doing with the animals.

12 Many more of these behavioral
13 tests are automated using motion sensor boxes,
14 light detector, behavior -- oh, infrared
15 boxes, there are a great deal more
16 automation -- automated systems going into
17 these to do high through-put screening of
18 behaviors for these -- that have been
19 developed for the neurogenomic studies because
20 of the -- what I'm thinking of specifically
21 are the ENU genomic screening systems. So --

22 DR. PORTIER: I think this is

1 good.

2 DR. HORTON -- in terms of looking
3 at low doses, I think many -- mainly it's
4 because many of the developmental effects may
5 be sensitive to lower doses than adult
6 response, and you just don't know what you're
7 going to pick up when you start looking at the
8 low doses because those experiments haven't
9 been done yet.

10 DR. PORTIER: I have a follow-up
11 question for the Agency. If atrazine were
12 newly registered today, and hadn't been around
13 for 50 years, would a neurodevelopmental or a
14 neurotox battery be required of the registrant
15 as part of the standard package? I mean would
16 we have had something like that in the
17 standard packet?

18 DR. MENDEZ: Elizabeth Mendez,
19 EPA.

20 Within the last two years the new
21 CFR, the new Code of Federal Regulations, we
22 have a new set of guidelines, and under those

1 conditions an acute neurotox would have been
2 required. A DNT is still not, and a
3 subchronic as well. So an acute adult
4 neurotox and a subchronic neurotox would have
5 been required. A DNT is still a tier two
6 test, and DNT is the developmental neurotox.

7 DR. PORTIER: Dr. Chambers.

8 DR. CHAMBERS: There are plenty of
9 objective measures in behavioral tests, so
10 that's -- it's not all fuzzy subjective stuff.
11 With all due respect, I'm going to disagree
12 with you. I know that resources and time and
13 everything is really limited, and I don't
14 really see anything in the data sets that we
15 were provided with that suggest that doing
16 some extensive developmental neurotoxicity,
17 not DNT testing, but any kind of extensive
18 developmental neurotoxicity testing would
19 really be a wise use of time and resources
20 right now considering the much more extensive
21 database you have already presented to us on
22 the neuroendocrine effects.

1 So I don't think there's really
2 anything suggestive in those particular papers
3 that were given to us that suggest a very
4 extensive array of neurotoxicity testing is
5 done. I'm just a little bit afraid that it
6 might be nothing more than a fishing
7 expedition and that you would not find
8 anything at lower doses that would, again,
9 displace the neuroendocrine effects as the
10 most sensitive effect right now.

11 DR. PORTIER: And so there's the
12 other issue though is the developmental versus
13 adult. All right. I mean part of what I hear
14 Dr. Horton saying is developmental
15 neurobehavioral and so the question is whether
16 the endocrine data and endpoints are
17 sufficient at the developmental stage. I
18 mean, you know what I'm kind of saying?
19 Because most of the studies we've looked at
20 are adult animal studies. Right?

21 DR. CHAMBERS: Well, a couple of
22 these -- this is Jan Chambers again -- a

1 couple of these were early treatments, but
2 they were not well-powered for the
3 statisticians, they were not well-conducted,
4 you know, not standard types of tests and all.
5 So, again, the data are not good in terms of
6 dose responses and so forth. So, again, you
7 know, in my mind, I didn't see anything that
8 really suggested that we should rush right out
9 and expand these types of studies.

10 DR. PORTIER: I guess it's my
11 understanding there'll be more data coming on
12 some of that as well. Right? Some of the --

13 DR. MENDEZ: That is correct. We
14 have more data coming in within this week.

15 DR. PORTIER: Dr. Horton.

16 DR. HORTON: Yes, well, one of the
17 areas where we disagree is over the quality of
18 the data. And I guess the metaphor here is
19 whether you are feeling the elephant in the
20 room or not. And while each individual study
21 is not of high quality, when you look at each
22 of these individual studies, I'm feeling an

1 elephant in the room that suggests that there
2 may be something going on in terms of the
3 effect on the nervous system.

4 And each of the nervous -- the
5 neural systems that is impacted or suggested
6 to have -- to be influenced by atrazine in
7 these systems, the dopamine system, the
8 serotonin system, the -- what do we have in
9 here, the somatostatin system -- not so much
10 the somatostatin because that is influencing
11 growth hormone, but it feeds back in there
12 someplace, but primarily serotonin and the
13 dopamine systems. And as you look at how
14 widespread those areas are, when you think of
15 their impact on cognition, when you think on
16 their impact on affect and attention.

17 You need to consider not just what
18 impact they may have on reproductive function,
19 on the HPA axis, you need to consider what
20 impact they have on mental disorders,
21 schizophrenia, affective disorders, executive
22 function disorders. There's a wide range of

1 issues.

2 You need to consider the
3 relationship between estrogens and their
4 inter-relationship with insulin signaling and
5 metabolic disorders. We're walking into
6 potentially a broad range of effects. There
7 are insulin receptors in the brain. Anybody
8 who had physiology or biology 20 years ago
9 probably thinks of glucose and insulin,
10 insulin not having an effect in the brain, and
11 glucose uptake being constant in the brain.

12 Well, that's true, but there are
13 insulin receptors in the brain, and those
14 insulin receptors are interacting with
15 estrogens, and they're influencing the
16 signaling in the brain. So as I feel this
17 elephant in the room, and I feel the dopamine
18 system potentially being influenced, I think
19 we need to look at this.

20 And when I look at graphs that,
21 yes, they have small sample sizes, and the
22 data were collected by stereology, which may

1 or may not have wide acceptance, but the
2 stereology is a relatively new and highly
3 sophisticated method for collecting data. It
4 requires exceptionally expensive confocal
5 microscopes, which are on the order of tens of
6 thousands of dollars. It requires
7 considerable training in using that microscope
8 to analyze the micrographs. These are not
9 simple techniques.

10 Or I consider that journal editors
11 consistently require people to cut down the
12 amount of images that they put into papers.
13 I'm not disillusioned or concerned when
14 there's not a micrograph in a paper. But when
15 I do see that an author has given me not just
16 the bar graph and the standard error of the
17 mean, but they have given me the scattergram
18 that includes every individual point for the
19 animal so that I can compare the distributions
20 for myself and look at the overlap and see
21 what those data look like, and know what that
22 elephant in the room feels like.

1 I'm willing to think that we do
2 have an elephant in the room, and I think we
3 need to accept that we have an elephant in the
4 room. And I think we need to evaluate the
5 effects of atrazine on the brain in multiple
6 situations. Thank you.

7 DR. PORTIER: I think what I'm
8 going to recommend to Dr. Horton and Dr.
9 Chambers and Dr. Reed is when we put this
10 together, we don't necessarily need consensus,
11 but we need all of these arguments kind of
12 filled out. And I think you've done that. So
13 I'm not worried about coming to consensus on
14 this one. I pushed, but it's clear that we're
15 not going to get the panel to agree on this.

16 And I get the feeling Dr. Horton's
17 on one side, Dr. Chambers is kind of on the
18 other, and Dr. Reed's kind of in the middle.
19 So we'll be looking at Dr. Reed to kind of
20 build that transition between the two.

21 Any additional comments on this
22 question?

1 DR. REED: I was asked if I'm
2 ambivalent. No, I'm not ambivalent for being
3 in the middle. Yes, but I think, you know, my
4 comments were --

5 DR. PORTIER: No, I think of you
6 more as cautious and unwilling to give up on
7 these potential health effects --

8 DR. REED: Right. Right.

9 DR. PORTIER -- as a potential
10 point of departure.

11 DR. REED: Right. And the concern
12 was really just based on the mode of action,
13 as we've been talking about these two or three
14 days, and in addition there might be, you
15 know, other sidebar on the mode of action
16 which is not completely deciphered, but I am
17 concerned about developmental type of effect
18 with in utero exposure, perinatal exposure,
19 and the sensitivity issue in that I think it
20 needs to be addressed.

21 DR. PORTIER: And it will be.

22 Yes, Dr. Lowit.

1 DR. LOWIT: I would, unless Dr.
2 Cooper has something -- or Dr. Mendez had
3 something to add, I would, I guess, follow
4 your line of thinking to have the report
5 represent the variety of opinions, and I guess
6 putting a happy face on coming back two or
7 three more times.

8 We do have the September meeting,
9 and I'm not aware that anything new will come
10 up on this issue, but we may be able to, when
11 we have a newer set of points of departure and
12 a fuller evaluation of the life stage effects,
13 this may become -- there'll be more clarity
14 with a more full analysis around the
15 relationship of all these, and we can make a
16 more robust description, I think.

17 DR. PORTIER: Okay. I think we'll
18 close out on this question. That ends
19 Question 1.6, and we're going to move on to
20 Question 1.7.

21 DR. COOPER: I'll read this
22 question. I'll keep the ball moving anyway.

1 Charge Question 1.7, based on a
2 review of two studies of the potential effects
3 of atrazine on the prostate, Section 3.3.2.2
4 of the draft issue paper, the Agency has
5 concluded that the results of the Rayner, et
6 al., study 2007 -- the Rayner, et al., 2007
7 study of pregnant rats treated during
8 gestation support previous observations,
9 Stoker, et al., 1999, that atrazine treatment
10 to the rat dam either perinatally or early
11 postnatally can increase prostate weights due
12 to an increase in inflammatory infiltrate in
13 the male offspring.

14 This effect on the offspring was
15 shown to be due to a suppression of prolactin
16 in the atrazine exposed dams during
17 lactation -- which I might add is in contrast
18 to the Stoker paper where it was done
19 postnatally -- and is consistent with the mode
20 of action of atrazine on neuroendocrine
21 function.

22 The Agency also preliminarily

1 concluded that further research is needed to
2 provide more convincing evidence that
3 atrazine-mediated suppression of prostate
4 cancer in the probasin/stroke SV40T antigen
5 transgenic rat, androgen-dependent prostate
6 cancer rodent model, may possibly be due to
7 caloric restriction rather than endocrine-
8 related as postulated by Kandori, et al.,
9 2005.

10 Please comment on these
11 preliminary conclusion regarding the recent
12 prostate findings. Please comment on the
13 extent to which available data support the
14 proposed mode of action for prostatitis, and
15 the appropriateness of the rodent model in the
16 context of human health.

17 DR. PORTIER: Dr. Williams.

18 DR. WILLIAMS: So this question
19 gives us some questions about studies that we
20 really haven't talked about at all yet, so I'm
21 just going to briefly review the two studies
22 in question and then answer these.

1 So the Stoker, et al., '99 paper
2 demonstrated that postpartum administration on
3 day 1 to 4 postpartum of doses between 6 and
4 50 milligrams per kilogram per day of atrazine
5 to lactating rat dams dramatically, or in the
6 higher doses completely, inhibited suckling-
7 induced prolactin release in the dams, and
8 that it also caused an increased incidence of
9 lateral prostate inflammation in the male
10 offspring at four months of age.

11 They observed the same effect
12 after treating dams with bromocryptine, which
13 is a dopamine agonist that inhibits prolactin
14 release. And this effect was reversed by the
15 administration of prolactin to the atrazine-
16 treated dams. So they basically saw an effect
17 and they also reversed the effect, and so it
18 was a really very nice study in that way.

19 The proposed mechanism to explain
20 these results was that prolactin is important
21 for neonatal brain development, and lack of
22 neonatal prolactin exposure from getting

1 prolactin in the milk leads to a failure of
2 dopaminergic system development -- again,
3 we're talking about this sort of neonatal
4 effect on the brain here -- and eventual
5 hyperprolactinemia in the adult male.

6 The study didn't actually
7 demonstrate hyperprolactinemia, this was based
8 on previous work where that had been shown,
9 that hyperprolactinemia can occur at about the
10 one month old male after this kind of an
11 exposure. And the prolactin levels were only
12 measured at four months of age, and at this
13 time there was no further hyperprolactinemia,
14 so they were different from controls at that
15 point. But the proposed mechanism was that
16 there was this period of hyperprolactinemia
17 that led to prostatitis.

18 So the newer studies, Rayner, et
19 al., in 2007, examined whether treating rat
20 dams with 100 milligrams per kilogram per day
21 of atrazine during late gestation, in day 15
22 to 19, had adverse effects on prostate

1 development of the male offspring at either
2 four or seven months of age. And in this case
3 they actually used a cross-fostering design to
4 distinguish between direct effects of prenatal
5 exposure of the atrazine that's given during
6 gestation, or was if effects of the prenatal
7 exposure to atrazine on the mom with milk, and
8 so the cross-fostering design was used. And
9 so they basically took pups from controls and
10 had them suckling from the previously
11 atrazine-treated animals, and then they also
12 some atrazine -- animals from atrazine-treated
13 dams that were moved over to control animals.
14 So it was a really nice cross-fostering study
15 in that way.

16 So this study demonstrated a lot
17 of similar things, that they -- suckling from
18 an atrazine-exposed dam resulted in an
19 increased incidence of prostatitis, whether or
20 not the male was exposed prenatally to
21 atrazine. So it looks like it's a postnatal
22 effect that is the sensitive time, not

1 prenatal. And that was consistent with the
2 Stoker findings where they only treated
3 postnatally and got the effect. Here if the
4 pup didn't suckle from the atrazine-treated
5 mom, there was no effect. So if they went
6 over to the controls, they did not have the
7 prostatitis.

8 So regarding the proposed mode of
9 action, the Stoker results demonstrate a clear
10 connection between diminished maternal
11 prolactin levels and prostatitis in the male
12 offspring. However, the proposal that the
13 prostatitis was due to hyperprolactinemia in
14 the male offspring wasn't tested in these
15 studies, as I mentioned. The prolactin levels
16 were only measured at termination of the
17 experiments at 120 days of age and were no
18 different from controls at that time. They
19 clearly could have been elevated earlier on,
20 and that just wasn't measured here.

21 One way to test that question
22 would be to follow prolactin levels and

1 document that indeed they are elevated during
2 some time of the peripubertal period, or
3 potentially blocking hyperprolactinemia at
4 that time by administering bromocryptine to
5 see if that's actually the mechanism to
6 explain the prostatitis because there's also
7 the possibility that there were atrazine
8 metabolites or something in the milk that the
9 pups were exposed to, and that these
10 metabolites might have affected the brains
11 directly or done something else that led to
12 the prostatitis later.

13 The reason that this matters is
14 because it would be important to know if it's
15 something in the milk that's a problem or
16 something not in the milk that's the problem
17 if we're going to think about human health
18 effects later. For example, if the problem
19 was related to diminished prolactin levels in
20 the milk, then maybe we ought to be worrying
21 about the effects on human health of failure
22 to breast feed, which is true of about 30

1 percent of women in the United States.

2 On the other hand, if it's
3 something due to having atrazine metabolites
4 or something else in the breast milk, we need
5 to worry about the 70 percent of women who are
6 breast feeding. And so, kind of getting back
7 at is it really important to figure out the
8 mechanism in this particular case, it may be
9 because it'll affect how we're going to think
10 about the exposures to the pups.

11 So now I'd like to move on to the
12 Kandori findings where the Kandori paper,
13 looking at prostate cancer and the
14 probasin/SV40T antigen-transgenic rat, the
15 paper basically supported the idea that
16 atrazine-mediated suppression of prostate
17 cancer in this model was due solely to caloric
18 restriction and not -- and was not an
19 endocrine-related outcome.

20 And I think that's an important
21 question given that there is a lot of
22 literature where, at least in the high-dose

1 atrazine studies, there is clearly a caloric
2 restriction effect, where given high enough
3 doses, animals will lose weight and maybe the
4 weigh loss could end up explaining findings
5 later.

6 Unfortunately, there's a lot of
7 problems with this particular study, and so I
8 think at the end the Agency's conclusion that
9 it's leading you to uncertain findings is
10 generous at best. And there were four
11 problems that I'll outline. One is that the
12 atrazine dose that was administered is very
13 uncertain in these studies. They were using
14 dietary administration, they had two rats per
15 cage, they don't really know what each rat
16 got. And the diets, when they went back and
17 measured what the diets actually had in them,
18 they didn't have in them what they thought
19 they had put in them in the first place, and
20 so the intake couldn't really be calculated.

21 The testosterone levels that they
22 saw in these rats were not different, even

1 though they had similar doses, where in other
2 studies testosterone levels were different in
3 the atrazine-treated animals. But the
4 atrazine dosing might have been so variable
5 that you couldn't find results. The
6 testosterone levels had standard error bars
7 that were basically as large as the bars
8 themselves. And so it was just a lot of
9 variability, it was so hard to make a
10 conclusion.

11 The caloric restriction group
12 themselves had highly variable testosterone
13 measurements, and so was it caloric
14 restriction and other issues with that, or was
15 it something to do with the testosterone.
16 It's really not clear. And then at the end of
17 the day this was a model where 100 percent of
18 the animals have adenocarcinoma or other -- or
19 intraepithelial neoplasia in the prostates at
20 15 weeks of age. These were looked at 13
21 weeks of age, and indeed pretty much 100
22 percent of the animals had the problem.

1 What they showed was that with
2 either the atrazine or the dietary restriction
3 and caloric intake there was a very, very
4 slight decreased if you measure the number of
5 epithelial cells as a ratio of epithelial
6 cells to total prostate size. And it was a
7 very small change and it was not a change in
8 overall levels of cancer at all. And given
9 that they only did these measurements on
10 literally two slices through the prostate and
11 they didn't do serial sections that encompass
12 the entire prostate, the findings were so
13 minimal that I'm not real enthusiastic that
14 another person doing the exact same study
15 would come up with the same results.

16 So interesting idea, potentially
17 could complicate studies if you have to think
18 about caloric restriction, but I'm not sure
19 that this particular study should be given
20 really any weight in terms of what the EPA
21 decides to do.

22 So regarding the appropriateness

1 of a rodent-model in the context of human
2 health, there really is a consistent finding
3 in both rats and humans of an association
4 between prostate inflammation and
5 proliferative inflammatory atrophy lesions,
6 prostate hypertrophy, intraepithelial
7 neoplasia, and cancer. And there's enough
8 findings in human literature in that regard
9 that there's actually been clinical trials
10 looking at non-steroidal anti-inflammatory
11 agents for the attenuation or treatment of
12 prostate cancer.

13 So the link is really strong in
14 the human literature, and certainly it seems
15 to be just as strong where prostatitis is seen
16 in association with prostate neoplasias in
17 rats. So there's a lot of similarities to the
18 two systems, and I think that that says that
19 it's a reasonable model.

20 In terms of thinking about
21 prolactin exposure -- sorry, loss of prolactin
22 exposure and effects through lactation, I

1 think we need to know a lot more about the
2 mechanism before you can say that's a
3 reasonable model.

4 DR. PORTIER: Thank you.

5 Dr. Delclos?

6 DR. DELCLOS: I'm in agreement
7 with those comments, and I really have nothing
8 further to add.

9 DR. PORTIER: Dr. Horton.

10 DR. HORTON: I'm in agreement, and
11 I have nothing to add.

12 DR. PORTIER: Somebody else,
13 please? Dr. Heeringa agrees.

14 Dr. Cooper.

15 DR. COOPER: Just to follow up one
16 thing. There's, again, the time line's a
17 blur, but I don't believe this was post-2003.
18 We had a graduate student working in my lab
19 who essentially followed through on that. The
20 hypothesis that was being examined, it was
21 based on Crowley's work earlier on, was that
22 if you inhibit prolactin, tubular and

1 fundibular dopaminergic neurons won't mature.

2 And that was based on a number of different
3 studies where they showed if they're not
4 there, they don't get momma's prolactin.

5 And so what Chris Langdale did,
6 and this is his thesis work, which is through
7 NC State tox department, he showed that the --
8 he looked at the dopaminergic neurons'
9 developing, and indeed there was a delay.

10 Where the change occurred most dramatically in
11 terms of prolactin regulation was between
12 PND27 and 35, peripubertal change. And it
13 occurred only at that time, and that matched
14 very well back with some of those -- Judy
15 Ramelay's work looking at maturation of
16 prolactin regulation.

17 So there was some mechanistic --
18 again, these are piecemeal things, but I think
19 they're supportive of that, or point in the
20 direction that there may be impairment in that
21 titis system based on that kind of exposure.
22 And whether that is an impact -- these neurons

1 grow -- they mature up to birth and then they
2 require the mother's prolactin, so whether the
3 preterm treatment is going to influence her
4 ability to release prolactin and then that's
5 something that I don't believe has been
6 followed through,

7 So, no, we didn't measure both
8 before and after birth, but mechanistically
9 anyway it's -- the data that Chris Langdale
10 had was consistent with that dopaminergic
11 hypothesis. I think it speaks somewhat to
12 this do we see developmental effects. I
13 believe we've looked for developmental effects
14 that maybe looking under the light, but
15 they're there.

16 DR. PORTIER: Dr. Horton.

17 DR. HORTON: Dr. Horton. I was
18 just going to comment, but Dr. Cooper said it
19 for me, is that what he just said about the
20 prolactin changes in these developing males
21 points to a developmental effect of the
22 atrazine on the dopamine neurotransmitter

1 system, which is relevant to Question 1.6.

2 DR. PORTIER: I don't see any
3 additional comments, and I can't really
4 summarize her summary, which was pretty good.
5 So we'll make sure that's in the report.

6 Okay. Gosh, I was thinking we
7 might not get to the hydrology today. So take
8 your time reading Question 1.8.

9 DR. LUEBKE: Okay. On to Question
10 Number 1.8. Based on data obtained in studies
11 to assess the effects of atrazine on the
12 immune system following developmental and
13 adult exposure, as well as in vitro
14 mechanistic studies, EPA concluded that
15 atrazine has the potential to affect the
16 immune system. However, the Agency has also
17 concluded that underlying mechanisms of
18 atrazine-mediated immunotoxicity -- you'd
19 think I could say that word by now -- and its
20 relevance to potential adverse health effects
21 in humans are still not thoroughly understood.
22 It is well established that products of the

1 endocrine system modify immune function.
2 However, adult rodent studies have not
3 determine whether immune system effects are
4 caused by direct effects of atrazine and/or
5 its metabolites, or whether they are the
6 result of modulated endocrine hormone
7 production, which in turn affects immune
8 cells.

9 Two published studies indicating
10 that exposure to atrazine during immune system
11 development may result in altered immune
12 functions in offspring. Although no
13 conclusions were drawn on the potentially --
14 on the potential adversity of these effects
15 because immunosuppression was observed in one
16 study and immunoenhancement was observed in
17 the other.

18 Please comment on the potential
19 explanations for the disparate findings
20 reporter by Rooney, et al., and Rowe, et al.
21 Many immunotoxicologists consider
22 immunomodulation -- i.e., suppression or

1 enhancement of immune function -- as a
2 potentially adverse alteration of homeostasis
3 because both have been associated with disease
4 states. Thus, while the results of Rooney, et
5 al., and Rowe, et al., may appear to be
6 contradictory, together the data indicate
7 unintended immunomodulation at approximately
8 the same dose in two species.

9 Please comment on the effects of
10 gestational atrazine exposure as
11 immunomodulation when describing the
12 immunotoxicological outcome of developmental
13 immunotox study -- immunotoxicity studies.

14 Appendix -- shall I keep going?

15 Okay. Appendix B of the draft
16 issue papers describes experiments conducted
17 by EPA scientists on the potential
18 developmental immunotoxicity of atrazine. The
19 results for the experiments provide
20 conflicting results. Additional studies did
21 not provide a suitable explanation of the
22 differences. The Agency believes both sets of

1 data are of high quality. However, in the
2 context of hazard assessment, such differences
3 are difficult to interpret. Please comment on
4 the information contained in Appendix B and
5 provide suggestions for interpreting such data
6 as part of the atrazine re-evaluation.

7 Oh. Oh, okay. Here we go. We're
8 having so much fun.

9 The available data -- this is a
10 long question too -- the available data do not
11 indicate that atrazine-induced immunotoxicity
12 is a more sensitive endpoint than the
13 atrazine-induced effects on neuroendocrine
14 function, e.g. attenuation of LH surge and
15 estrous cycle disruption which form the basis
16 for the current chronic RfD in female Sprague-
17 Dawley rats. Please comment on the degree to
18 which these preliminary conclusions are
19 supported by the available data.

20 DR. PORTIER: Dr. Holladay.

21 DR. HOLLADAY: The text for that
22 question was longer than any others. We ought

1 to petition for a higher per diem or something
2 for that.

3 Ken, we talked as a group about
4 addressing each sub-question, I think there
5 were four in here, one at a time and maybe it
6 being more functional if we did it that way.

7 The first of those is the Appendix
8 B question, which Dr. Luebke covered very well
9 the day before yesterday, I think it was. So
10 I'll just review that very briefly. These are
11 the Rooney, et al., studies where the
12 hypothesis that atrazine may cause
13 developmental immunotoxicity through
14 disruption on prolactin or thyroid hormones
15 was tested in Sprague-Dawley rats using a dose
16 of 35 milligrams per kilogram per day by oral
17 gavage. This is from gestation day 10 through
18 postnatal day 23, I think it was. And they
19 chose that dose to be just above the NOEL for
20 delayed onset of puberty in female offspring.

21 They had separate groups exposed
22 to bromocryptine and to propylthiouracil to

1 produce hypoprolactinemia and hypothyroidism
2 respectively. Neither of those two groups
3 caused immunosuppression in the offspring.
4 The experiments were replicated twice. The
5 offspring did show immunosuppression at about
6 eight to nine or ten weeks of age. The
7 atrazine decreased the primary antibody
8 response to sheep red blood cells and
9 decreased the delayed type hypersensitivity
10 response in adult male, but not female,
11 offspring.

12 I think these tests were probably
13 chosen or selected in part from the National
14 Toxicology Programs Risk Assessment for
15 Immunotoxicity and positive data would predict
16 a positive response also in challenge assays
17 if we were to proceed that way. So it's a
18 good testing, good experimental design. I
19 read the papers, I put in the graphs. The
20 suppression looked real and I think it was at
21 about 56 to 59 percent of the control level.

22 You can ask questions were p-

1 values -- was chance playing a role in this
2 one time out of 20, will p-value let you down
3 just because of the level we set? I don't
4 think that's the case, but with one chance out
5 of 20, and then in a replicate experiment
6 multiplying that it shouldn't occur more than
7 one time out of 400 twice in a row on you for
8 one assay, and then we've got the DTH as a
9 second assay that did the same thing, the
10 experimental design looked good, the data
11 looked real. The authors concluded that
12 developmental exposure to atrazine caused a
13 gender-specific suppression of immune function
14 in the adults that didn't appear to be through
15 prolactin or thyroid hormone, the mechanism.

16 So that's an overview for the
17 studies. The difficulty that we were asked to
18 consider came from the further repeat of these
19 studies when the lab was moved from old EPA
20 facility to the new one across the lake from
21 NIEHS, and then didn't replicate for the
22 investigators in spite of same protocol, same

1 lab people doing the assays. So 35 milligrams
2 per kilogram per day was the high dose
3 selected in the repeat study, the same as the
4 first study. Lower doses of 17-1/2 and 3-1/2
5 milligrams per kilogram per day were used.
6 This was an attempt to establish a dose
7 response for the effect observed. End data
8 were negative.

9 Second experiments used Sprague-
10 Dawley, Long-Evans, and Wistar rats to look
11 for a strain effect. Strain differences data
12 were, again, negative. The assays were
13 conducted only in males given the results in
14 the first set of experiments. So the
15 investigators concluded that some unknown
16 environmental factor was probably behind the
17 difference in response. They have a high
18 level of confidence in the technical soundness
19 of the published studies.

20 From my review of those, I see no
21 reason to think otherwise and agree with this
22 unknown environmental factor. I think it was

1 Dr. Akana who suggested that vibration in a
2 new facility or something like that could play
3 a role. I know last week someone from the lab
4 came to my office with those conical
5 centrifuge test tubes we hold our cells in,
6 the orange-topped ones, and said these were
7 from the last two batches we'd gotten.

8 Opened one and he said, smell it,
9 and I smelled it. I said, I don't really smell
10 anything. He said, Okay. Opened the next
11 one, he said, smell this one. It smelled like
12 a plastics factory or a new car or a carpet.
13 And he said, I've never smelled that in these
14 before, but I'm afraid that could skew our
15 data, whatever these things are emitting could
16 be harmful to ourselves, and he was concerned
17 enough he called the vendor, who said, Yes,
18 we've outsourced our production to Mexico.

19 Don't know what the difference
20 was, but sometimes there are little things
21 that do this to us that cause differences like
22 this. Unknown environmental factor was a good

1 disclaimer, I think, for that, and we get
2 caught in it now and then. So my conclusion
3 is there's no reason to doubt the results of
4 either study in this case, and I think the
5 original study was conducted appropriately and
6 the results should be accepted as real under
7 the conditions of that study.

8 DR. PORTIER: Okay. Done with the
9 first part.

10 DR. REGAL: Right. So with regard
11 to the Rooney study --

12 DR. PORTIER: Dr. Regal.

13 DR. REGAL: With regard to the
14 Rooney study, everything looks very sound in
15 terms of methods, techniques, design, and, you
16 know, clearly a critical parameter has not yet
17 been defined to explain why it can't be
18 replicated in another status.

19 DR. PORTIER: Dr. Bucher.

20 DR. BUCHER: So I'm not an
21 immunotoxicologist, but I do have the pleasure
22 of having attracted Andy Rooney to our program

1 from EPA, so I talked to him about these
2 studies, and I just wanted to have a
3 placeholder in case the discussion went off in
4 an area where he would have disagreed with
5 some of those conclusions, but he agreed with
6 everything that has been said about those two
7 studies -- and that they were, in fact,
8 excellent studies and just for some reason
9 didn't repeat. So I agree with those
10 comments.

11 DR. HOLLADAY: All right. So
12 Holladay back. Now the second question we're
13 asked to address was the dichotomy, if you
14 will, between the Rooney, et al., results 2003
15 and Rowe, et al., 2006. The difference
16 between these studies on one reported
17 postnatal immune suppression, one reported
18 enhanced immune responses. These are in the
19 adult offspring after the developmental
20 exposure.

21 I think the most important thing
22 to consider between these two studies is that

1 there were many differences between
2 experimental design. The Luebke lab used the
3 Sprague-Dawley rat and out-bred animal; the
4 Rowe, et al., studies, which is John Barnett's
5 lab in West Virginia, another internationally
6 recognized laboratory, both the laboratories
7 are of that stature, used Balb/c mice. So
8 we've got different experimental animals. The
9 Balb/c mouse is a T helper 2 skewed mouse
10 which is skewed towards enhanced antibody
11 production. So that's one difference that's
12 important.

13 Exposure route is also important.
14 The Sprague-Dawley rat study is oral gavage,
15 which provides a bolus or spike exposure of
16 the atrazine to the pregnant animals. The
17 Barnett lab used implants that provided a
18 lower level time release. The doses were
19 comparable. The Rowe, et al., studies
20 calculated their dose varied from about 35 to
21 23 milligrams per kilogram per day atrazine.
22 This is in the mice, again, from gestation day

1 10 to 12, so this is a shorter exposure as
2 well.

3 So both studies were well
4 designed, in my mind, robust, used statistical
5 power analyses to calculate the needed N. The
6 Barnett study used N of 11 group size, which
7 is larger than I've tended to use in a study
8 like this.

9 So the results are seemingly
10 different, but when we consider the endpoints
11 evaluated, when we consider the models, I'm
12 not sure they are -- well, it's not worrisome
13 to me that they're different. I commented the
14 other day to that we're seeing more results of
15 this sort, even within strains where we see
16 both immune suppression and immune enhancement
17 coexisting in the same animals.

18 It was kind of a paradox when we
19 first realized this was happening, but it
20 does. DTH, delayed-type hypersensitivity, or
21 T cell response might be depressed, while
22 other T cell activities are skewed or

1 enhanced.

2 So we've got genetically different
3 animals and one is showing a depressed T cell
4 response, the DTH response in the rat study,
5 and others showing an enhanced response in the
6 mouse study, the MLR or proliferation, T cell
7 proliferation outcome, and the cytotoxic T
8 lymphocyte activity and other T cell activity,
9 as well as enhanced antibody production. So
10 different results but very different models,
11 results not inconsistent with literature in
12 other mouse models with different chemicals.

13 So as the Charge Questions
14 indicated, there are seemingly different
15 results, but in my opinion these should, at
16 this time, be both considered as observations
17 that represent true outcomes for the models
18 and experimental systems used.

19 DR. REGAL: Jean Regal. I
20 definitely agree, I just have a couple of
21 differences to add for the record in terms of
22 the end result. They were looking at eight

1 week old rats and 12 week old Balb/c mice as
2 to their timing, and I have no reason to think
3 that those are different in terms of being
4 post -- past sexual maturity. They used two
5 different vehicles, time-release pellets
6 versus methylcellulose gavage. Again, no
7 reason to believe there would be a difference.

8 One question I would have for
9 people who think about atrazine metabolism is
10 would the metabolism differ depending on the
11 route of administration, i.e. one gavage
12 versus sub-Q administration? Could some of
13 the metabolites be, you know, causing an
14 immunoenhancement versus some an
15 immunosuppression? So I guess I'll be
16 looking -- and any comments people have on
17 that would be appreciated.

18 And the only other -- one other
19 thing in terms of the rat study, there was a
20 very small decrease in weight of the seven day
21 old rats, and with the Balb/c mice there was
22 no weights at birth so the very small chance

1 that any of this might be -- have been done to
2 intrauterine growth restriction rather than an
3 effect of atrazine.

4 DR. BUCHER: So I have nothing
5 really to add. I do agree that while it would
6 have been nice if these changes would have
7 gone in the same direction, it doesn't
8 necessarily detract from the fact that they
9 are real effects, so.

10 DR. PORTIER: Well, why don't we
11 open up and see if there's any metabolism
12 comments.

13 Dr. Hayton.

14 DR. HAYTON: Yes, I seem to
15 remember the McMullin 2007 paper which was a
16 physiologically-based PK modeling study, and
17 it's far from definitive, but the kinetics
18 suggested that there was a very substantial
19 pre-systemic elimination for the oral route.
20 And so that I think more than -- something
21 more than 60 percent of the atrazine was
22 converted to metabolites pre-systemically.

1 Well, that clearly wouldn't happen following
2 subcutaneous administration. So there
3 definitely could be route of administration
4 differences in metabolite exposure.

5 DR. GREENWOOD: I also came to
6 that sort of conclusion because for -- in
7 rodent studies, the profile for atrazine
8 itself is really a text book case of a
9 picture. It's consistent with a very low rate
10 of absorption and a rapid rate of elimination
11 and the production particularly of the diamino
12 chlorotriazine, which is sort of the end
13 product down that route.

14 The production of it was so rapid
15 that really I can't see any other explanation,
16 other than it was by the enterocytes. And
17 this has been seen for drugs and other things
18 that this happens.

19 And you get similar rates of
20 absorption in
21 humans. You can predict human absorption from
22 the rat pharmacokinetics, but the

1 bioavailability by the two is totally
2 different. So the rate of absorption is
3 similar and highly correlated in humans and
4 rats, but bioavailability by the oral route is
5 different. And the difference comes because
6 of this metabolism differential, metabolism in
7 the gut wall.

8 And it's something that's known,
9 really going back a long way where people used
10 C14-labeled phenols which were administered
11 orally and none of them reached the liver
12 intact, so where people were looking in the
13 hepatic portal vein. So it wouldn't surprise
14 me at all to different species and totally
15 different routes of application if you
16 wouldn't get totally different patterns of
17 detoxification products.

18 But what I would guess is, looking
19 at the -- I don't know whether the others
20 agree -- but looking at the profiles, it just
21 seem that this diamino chlorotriazine seems to
22 be the major detoxification end product. I

1 mean it was something like a hundred-fold
2 different -- higher than any of the other
3 compounds after that 24 hours.

4 DR. PORTIER: Dr. Horton.

5 DR. HORTON: Yes. One comment.

6 Even though we're considering the animals held
7 in a laboratory environment under constant
8 photoperiods and that laboratory mice are not
9 photoperiodic, some strains of laboratory rats
10 still show a photoperiodic response,
11 specifically the Fischer 344. And in other
12 species, specifically the dwarf hamsters,
13 Phodopus sungorus, they have been shown to
14 show photoperiodic dependent changes in their
15 immune response, and specifically the cellular
16 versus the humoral immune responses differ on
17 a seasonal basis.

18 So I'm wondering whether in
19 looking at these data, both the rat strains,
20 you know, Fischers versus Sprague-Dawley and
21 also the photoperiods might need to be taken
22 under consideration.

1 DR. SCHLENK: Yes, just to follow
2 up on the metabolism issues. I know -- I mean
3 as I mentioned earlier, there's some really
4 good evidence to suggest that it's a 3A4
5 substrate, which is actually expressed in
6 fairly high concentrations in the gut, so that
7 would argue for enteral metabolism immediately
8 without a systemic absorption at that point.

9 So there is that, although
10 recombinant proteins, I think the high -- the
11 more efficient catalytic pathways 1A2, which
12 would be more liver-based, but again, I think
13 arguing more for a -- if you do have 3A4 under
14 high KM, high sort of concentration-based
15 doses, then you probably would get the gut
16 metabolism preceding the hepatic.

17 DR. PORTIER: Dr. Luebke, you had
18 wanted to make a comment?

19 DR. LUEBKE: Okay. Well, I just
20 wanted to respond to a couple of things. So
21 photoperiodicity, a fellow that I know who's
22 done thousands and thousands of immunotox

1 studies took all of his mouse data from over
2 the years, just the control data, and he
3 graphed the antibody response and the delay
4 type hypersensitivity response, and what you
5 could see was sort of a nadir in the spring,
6 and as winter came on, it went up.

7 So mice are, indeed, photoperiodic
8 in at least -- you know, over the year. Over
9 the year. I shouldn't say photoperiodic.

10 Okay. So, yes, so there is annual cyclicity
11 in all that that can't be explained by seeing
12 sunlight because these things never see
13 sunlight unless they've just come out of the
14 truck.

15 The other thing that I would like
16 to mention is the issue of metabolism, and I
17 too was concerned with this and I thought that
18 there may be some questions about this because
19 of the different, very different routes of
20 exposure. And so I talked to Mike DeVito, who
21 used to be EPA and is now at NIESH and is
22 something of an expert on pharmacokinetics,

1 and he assured me that there would be massive
2 differences in the amount of atrazine, per se,
3 that was likely to be seen by these animals that
4 got the subcutaneous implant, because it's not
5 going through the gut, there is no first pass
6 through the liver, and if -- assuming that it
7 partitions into the blood and goes all over
8 the place, then, yes, there's going to be a
9 big difference.

10 But, now, Ralph and Tammy may have
11 to help me out of a quagmire if I start to dig
12 one here, but it's my understanding that if
13 you look at the parent and the metabolites,
14 that there are differences in the metabolites
15 in their action on the HPG axis and maybe the
16 HPA axis. If we assume that the effects that
17 we saw here are somehow related to that, and
18 not a direct effect of atrazine itself or it's
19 metabolites on the cells themselves, then it
20 would not be beyond the realm of possibility,
21 I think, that if you consider that what we
22 might see there, because of the differences in

1 dosing, might be something that's quantitative
2 and not qualitative, because if atrazine and
3 its metabolites are going to effect HPA to HPG
4 and then drive these different effects that we
5 see, then I don't think that they would
6 necessarily go in opposite directions.

7 And I had hoped that I could come
8 up with some different, you know, explanations
9 because it would be real nice to say, well,
10 yes, it's a metabolite thing and that's why we
11 got enhancement in one and suppression in the
12 other. But I still come back to the original
13 idea here that what we've got were unexpected
14 changes in function, neither of them
15 necessarily good.

16 DR. PORTIER: Dr. Greenwood.

17 DR. GREENWOOD: So I think that
18 sort of differences that you're looking at
19 would be larger in terms of exposure probably
20 to atrazine itself because it would much
21 higher, as I think has been said by the
22 implant. You're still going to get DSET

1 eventually formed as you go round the
2 circulation system, it comes through every
3 tissue eventually, and that's, you know, part
4 of the reason we look at the area under the
5 plasma curve as the opportunity factor for
6 reaching any particular tissue, whether it's
7 a target tissue or an non-target tissue.

8 But I think there are other
9 factors which can come into play as well
10 because if you have a high dose particularly,
11 then you start -- I think someone else alluded
12 to this yesterday -- you start to get
13 differences maybe in -- changes in the
14 glutathione pool, and as that's involved in
15 metabolism of all sorts of other things, then
16 you could start to produce different results.

17 And so I mean I haven't -- I would
18 need to -- really to see the sort of
19 concentrations people are getting from the
20 implants over the period of time compared with
21 the -- what you get by oral gavage. But oral
22 gavage is certainly something which is often

1 very difficult to interpret this sort of
2 absorption because the corn oil or the
3 methylcellulose forms part of the system, it
4 becomes part of the metabolic compartment, and
5 it changes with time.

6 So you get, you know, rapid
7 absorption initially, through for instance the
8 stomach wall, of what's free, and then it
9 takes time for the other stuff, particularly
10 with atrazine, I think, with its properties it
11 seems to stick to things, it takes longer to
12 disperse from the bolus. And so you get a
13 longer -- then a longer term lower level. And
14 if you've got metabolism as it's going through
15 the gut wall, then very little of the atrazine
16 itself is actually a component at very, very
17 low levels, and you won't get that if you've
18 got an implant. You'll have a more consistent
19 and prolonged level of atrazine.

20 DR. PORTIER: Dr. Reed.

21 DR. REED: Any reason to think
22 that male/female differences seen in any of

1 the studies could be explained by metabolism?

2 DR. GREENWOOD: Sorry. I haven't
3 seen that, anyway I've not seen any evidence
4 for such a difference.

5 DR. SCHLENK: This is Dan Schlenk.
6 Yes, as far as I know, I don't think there are
7 any male -- gender differences in 3A4 in rats.
8 I know there are the two -- family two
9 enzymes, but not necessarily the threes which
10 would be more appropriate for this, but.

11 DR. PORTIER: Okay. Back to the
12 question. Dr. Holladay.

13 DR. HOLLADAY: All right. Let's
14 continue. The third question was, Please
15 comment on characterizing the effects of
16 gestational atrazine exposure as
17 immunomodulation. This is rather than as
18 describing them as immunotoxic. And I think,
19 after what we've just said, that's the
20 appropriate descriptor, immunomodulating
21 allowing for both suppression and enhancement
22 of immune function after a developmental

1 exposure.

2 So I agree that's the correct
3 descriptor to use and agree with the Rowe, et
4 al., conclusions in their studies that this
5 potentiation of an immune response is an
6 important outcome, may potentiate diseases
7 such as auto-immune or hypersensitive
8 diseases, suggest the need to evaluate the
9 ability of developmental atrazine to enhance
10 postnatal immune responses in mouse models
11 that are genetically prone to express such
12 responses. So I have to wonder what would
13 happen in a mouse model that was genetically
14 predisposed to auto-immunity for instance.
15 That'd be an interesting question to have
16 answered.

17 So, yes, immune modulation is the
18 correct descriptor for these data.

19 DR. PORTIER: Dr. Regal.

20 DR. REGAL: Yes, I agree, with the
21 immune system, whether you get too much of it
22 or too little of it, it can be an adverse

1 event.

2 DR. BUCHER: This is John Bucher.

3 I also agree with that.

4 DR. PORTIER: Any additional
5 comments?

6 (No response.)

7 DR. PORTIER: It's a long
8 question, but you took it apart and answered
9 it. That's great.

10 Any comments from EPA? Oh,
11 there's one more. I'm sorry. It was a long
12 question. I only thought he had broken it
13 into three, and it's four.

14 DR. HOLLADAY: Maybe the most
15 important part. Do the available data support
16 immunotoxic, or immune system endpoints, or
17 immune modulation as more sensitive than the
18 atrazine-induced effects on neuroendocrine
19 function, the attenuation of the LH surge or
20 estrous cycle disruption. Please comment on
21 the degree to which these conclusions are
22 supported by the available data.

1 And I wrote as my opinion, I agree
2 that the available data indicate that
3 neuroendocrine reproductive effects are more
4 sensitive than immunotoxic or immune
5 modulation effects thus far detected. I
6 support the attenuation of the LH surge with
7 NOEL of 1 point milligrams per kilogram per
8 day as the appropriate point of departure from
9 the available data.

10 I just stress that it should be
11 considered the existing developmental
12 immunotoxicity database is quite limited and
13 further studies would be interesting. I think
14 neurodevelopment -- we could argue for more
15 development of immune system, we could certain
16 argue for more studies. But existing
17 database, I support the current point of
18 departure that we're using.

19 DR. REGAL: And I guess I do to
20 the same extent that -- except with the caveat
21 that with the developmental immunotox studies,
22 we really only looked at one dose, and

1 nobody's gone lower than 35 milligrams per
2 kilogram per day for 14 days, I think, or for
3 20 -- however many days they did it. And so
4 because of the disparate results there, and
5 because of -- to me I always try to remember
6 that in immunology stuff, you're going to see
7 bell-shaped dose response curves where you
8 have nothing with a lot, and nothing with a
9 little, but you get stuff in between. And so
10 we might not have hit those in between doses.
11 I think lower doses should be assessed
12 developmental immunotox-wise.

13 DR. BUCHER: And I agree with
14 those comments. I think that there was an
15 attempt to do a dose response study, but it
16 was not successful. But I think that that
17 certainly would strengthen the database, and
18 it's nice to see developmental studies, and
19 I'd certainly like to see them as well for the
20 neurobehavioral effects.

21 DR. PORTIER: I almost expect Dr.
22 Horton to jump in here. Anyone else on

1 metabolism? No? Yes, Dr. Akana.

2 DR. AKANA: I'd just like an
3 opinion from the metabolism crew on what
4 would -- what happens with atrazine when it's
5 mixed in the diet compared to say the gavage
6 delivery. Would you expect the same concerns
7 about the factions of metabolites of atrazine?

8 DR. PORTIER: Dr. Greenwood.

9 DR. GREENWOOD: Yes, I think that
10 if you've got a more continuous intake then
11 you're still going to get a very low
12 absorption from the diet. I think that the
13 atrazine, because it's very insoluble, it's
14 got to move out of the diet into the water
15 before it can cross -- there are several
16 barriers, there's the mucous layer and there's
17 the understood boundary layer, or the boundary
18 layer of water, not understood layer, the
19 boundary layer of water, and before it reaches
20 the epithelium.

21 And I think the key stage in all
22 of this, if you look at the papers of people

1 like Mike Abraham and so on, seems to be the
2 dissolution. And I guess actually the
3 kinetics of movement out of food will not be
4 too dissimilar from the kinetics of movement
5 out of the material that's used on oral
6 gavage.

7 But having said that, if it's in
8 the diet of course then it tends to be taken
9 over longer periods so you get a more --
10 rather than an acute exposure, as it were, you
11 get a longer term.

12 DR. PORTIER: Dr. Hayton.

13 DR. HAYTON: Yes, I agree with
14 what Richard Greenwood said. The other thing
15 I think that would happen is that there would
16 be a lower exposure rate because it's coming
17 in the diet continuously. And so to the
18 extent that there are these pre-systemic
19 effects by oral gavage, they could be
20 saturable because you give a fairly large dose
21 that gets exposed to that pre-systemic
22 machinery, whereas in the diet it would come

1 in at a much more -- at a lower level and at
2 a continuous rate, so.

3 And also the issue that Dr.
4 Greenwood brought up about glutathione pool
5 depletion, that may not happen extensively
6 either. So there's that possibility.

7 DR. PORTIER: Good question. Any
8 additional comments, questions?

9 (No response.)

10 DR. PORTIER: Okay. I don't see
11 any. I think what we're going to do is go
12 ahead and take a 15 minute break before we
13 jump into the big question of 1.9, and that'll
14 avoid anybody falling asleep in the mid-
15 afternoon slump. Right? So we'll be back at
16 2:45.

17 (Whereupon, the above-entitled
18 matter went off the record at 2:27 p.m. and
19 resumed at 2:50 p.m.)

20 DR. PORTIER: Let's get started.
21 We're going to dive into this last question of
22 Section 1, Question 1.9, which we've broken up

1 into kind of two parts, a risk assessment part
2 and a PK part, and we've got kind of two teams
3 that were assigned to answer those questions.

4 Just to kind of forewarn the
5 panel, we're not going to move on to Question
6 2.1 till tomorrow morning, but there are still
7 some clarification questions that the
8 hydrologists and the statisticians have about
9 the hydrology simulations, we we're going to
10 ask EPA and Syngenta to come back up for about
11 a half hour and see if we can kind of clarify
12 especially what those simulations were all
13 about so that we're really certain what they
14 did, and in hopes that that's going to make it
15 easier to us to answer the questions tomorrow
16 morning if we really know what they did.

17 My goal is to break a little after
18 4:30, early today. So, you know, in
19 compensation for yesterday. So -- I'm a mean
20 kind of person, but I'm very variable. Right?

21 So, Dr. Lowit, are you going to
22 read Question 1.9?

1 DR. LOWIT: Sure. And as you're
2 talking about the next steps and everything
3 else, just a little FYI to the panel, I
4 believe Drs. Cooper, Laws, Stoker and Luebke
5 will be either leaving tonight or first thing
6 in the morning, so you may not see them again,
7 or just for a little bit in the morning --
8 today at the meeting.

9 DR. PORTIER: That's a threat.
10 Okay.

11 DR. LOWIT: Yes. No. Oh, god.
12 They're going home. I'm just going to stop.
13 I'm just going to stop.

14 So if there are any lingering
15 technical issues that we've -- that are hazard
16 assessment related that we need to rely on
17 their expertise, we're just -- we may want to
18 do that before you cut off today.

19 With that, I will read Charge
20 Question 1.9. After the April 2010 SAP, the
21 Agency will evaluate the weight of the
22 evidence, what we call WOE, or woe, for

1 atrazine -- woe is us -- for atrazine by
2 integrating the experimental toxicology data
3 with the epidemiological studies. As part of
4 this work, the Agency will consider the
5 available data on hormonal changes and
6 functional outcomes that may be used as
7 endpoints for deriving PoDs, and that means --
8 that's what we mean by points of departure
9 that I talked about earlier -- across
10 different durations of exposure and for
11 different populations including potentially
12 sensitive ones.

13 Important studies evaluating the
14 dose response relationships for hormones
15 involved in the HPA axis are still ongoing.
16 These studies are expected to provide high
17 quality data that can be used to characterize
18 the entire dose response curve. With the
19 caveat that these data are not available now,
20 given the current understanding of atrazine's
21 mode of action, please comment on what would
22 be appropriate endpoints to consider for

1 deriving points of departure in a possible
2 future risk assessment.

3 And the second half, given that
4 the duration of the toxicological concern is
5 a key factor in evaluating the frequency of
6 drinking water monitoring, please include in
7 your response a consideration of the magnitude
8 and duration of changes in key events in the
9 toxicity pathway that are sufficient to
10 perturb normal function and comprise human
11 health. In defining the exposure window of
12 interest, please comment on the toxicokinetic
13 and dynamic considerations with respect to
14 atrazine's effects on the HPA/HPG axis.

15 DR. PORTIER: So you need to roll
16 it back to the first section. And I'll turn
17 it over to Dr. Reed, who has a strategy to
18 answer this question.

19 DR. REED: Right. When you don't
20 have the answer, ask.

21 Well, I thought I would give an
22 introduction. As Dr. Portier had said, that

1 I have a strategy, and he said it was okay.

2 I thought I would give an introduction and
3 maybe, you know, set the stage for input from
4 all areas, that I'm sure you are all storing
5 up this -- you know, something that you
6 couldn't say until now.

7 As we've been looking upstream, I
8 think, up until this point, upstream to the
9 pathway of toxicity to define the mode of
10 action, or actions, this issue question is
11 focusing us downstream to look at the key
12 events to define endpoints. And so by looking
13 downstream a little bit -- and it doesn't have
14 to be far, far downstream, it's really up to
15 you to define, this essentially connects us
16 back to the whole body physiology and systemic
17 toxicity, or systematic toxicity.

18 My definition, and you can all,
19 you know, put in your definition, my
20 definition of endpoint is the adverse health
21 effect that can be defined quantitatively with
22 respect to functional manifestation of

1 toxicological significance, or clinical and
2 disease expression such as age-specific
3 functions that are either compromised, or a
4 functional deficit or over-expression, or
5 perturbation of normal physiological
6 expressions.

7 So after I invite my fellow
8 discussants to go ahead first, as I said, I
9 would like to hear from every endpoint group
10 about what endpoints within your expertise
11 considerations that you would use, you know,
12 for point of departure for risk assessment.
13 We, early on, talked about this may be the
14 time or the place where the rubber meets the
15 road. If it were so, then I'd like us to all,
16 you know, put our heads together and it would
17 be going forward all-wheel drive, not just
18 front- or back-wheel drive.

19 The bruntness of the interest that
20 I expect to come out of this issue would
21 really reflect the complexity of addressing
22 the risk of an endocrine destructor with

1 complex signal pathways, and, you know, their
2 induction, their inhibition, and any other
3 possible mode of action that is non-exclusive,
4 or what was the -- general versus specific to
5 what we're interested in.

6 And instead of a shopping list, I
7 thought when you give your input, it'll be
8 good to keep in mind the sensitivity issue in
9 that risk assessment. We're looking for the
10 most sensitive endpoint with the assumption
11 that if you have taken care of -- or protected
12 against the most sensitive endpoint, then, you
13 know, the rest of this endpoint will not
14 occur.

15 And it would also help, now that,
16 you know, this morning you're heard about how
17 these endpoints are going to be used in risk
18 assessment, that if you have some sense of
19 sensitivity in terms of whether humans are far
20 more sensitive than animals pertaining to the
21 endpoint that you're thinking of, then it
22 would be nice to have that information too.

1 Just as a start off point, you've
2 heard the Agency coming with what they
3 currently have been using, and you have an
4 acute toxicity endpoint, you have the short
5 term, you have the intermediate term, so if
6 you want to give your input in such a -- you
7 know, sort of a duration context, that would
8 be good too. And keep in mind that the
9 pharmacokinetic/pharmacodynamic part will be
10 a separate part that you could put in your
11 input.

12 So with that, I just want to
13 remind you that -- I can't remember, this
14 morning or yesterday -- I think it's this
15 morning; such a long day -- I mentioned that
16 besides the endpoint male and female
17 reproductive and then we talked about hormone
18 surge, I mentioned this morning that in the
19 older risk assessment we were also looking
20 into some sensitive endpoints as expressed in
21 cardio type of effect: atrial fibrillation,
22 extra-medullary hematopoietic -- you know, in

1 spleen, that type of thing, and, you know, it
2 might fit in, it might not fit in, but just
3 put a context of that's what you see in the
4 whole animal study in the past where we just
5 don't have the mode of action, only looking at
6 the endpoints. And so maybe that picture will
7 be changed.

8 So with that, I will pass the --

9 DR. FENNER-CRISP: I think I've
10 been set up. Long, long ago, far, far away,
11 like over in Crystal City, there once was a
12 time when ATD staff was asked to do a
13 literature search and look for other
14 information in addition to the registration
15 package. They said, what? You want me to do
16 what? And it was really very difficult to
17 have that happen.

18 Obviously some things have changed
19 for the better, and in this particular case,
20 on an aspect of one chemical there are a lot
21 of additional data that have been assembled
22 and reviewed. I think yesterday or the day

1 before, and a couple of times today, though,
2 panel members have expressed some concern
3 about perhaps premature dismissal of some of
4 that information. There was some of that
5 conversation when talking about the
6 neurotoxicity, there was some of that
7 conversation yesterday when talking about some
8 of the cancer genotox data that were part of
9 this review. So I think one needs to be
10 mindful of that.

11 And in a comment today about --
12 we're really starting from scratch in the
13 reassessment. I interpret that to mean that
14 we're going to take another look at everything
15 we have, not simply all the stuff we've
16 concentrated on for the last few days, which
17 is really just one category, or all related to
18 kind of one category of information. There's
19 a whole lot -- if somebody were to bring in
20 the registrant's submissions and place them in
21 the middle of this four-sided table, the pile
22 of paper would represent a lot of trees and it

1 would probably exceed the height of the table.

2 So you have to be mindful of that.

3 Okay. So one of my comments would
4 be, remember that if one is actually doing a
5 reassessment from scratch, that one needs to
6 at least take a cursory view of all the
7 toxicity data from all the studies that are
8 part of the registration record and all of the
9 supplementary stuff that has been acquired
10 since, and revisit those and reconsider them
11 in the light of any new data that may be
12 available in these other domains, because it
13 might well be that something we didn't know
14 about, endpoints, particular endpoints may
15 have come to light through other work, not
16 necessarily atrazine specific. So that's my
17 first point.

18 In this particular case, we have a
19 number of new data sets and new parameters
20 with the further exploration of the mode of
21 action related to reproductive effects, which
22 also require a revisit, and we've talked about

1 that, of the prior assessment and make
2 decisions on whether or not to use what was
3 previously used in the risk assessment, or
4 whether or not some part of the new
5 information will become the focus of the risk
6 assessment for characterization of point of
7 departure, et cetera.

8 I would offer my opinion that the
9 appropriate endpoints for consideration for
10 deriving PoDs going forward would be the data
11 sets at each key event now characterized in
12 the mode of action. When we once had a set of
13 six or seven for the mammary tumor, and some
14 of those were overlapping with what was
15 thought about with respect to reproductive and
16 developmental toxicity, now there's another
17 whole set of data with -- related to HPA axis.

18 So given the definition of key
19 event, presumably there are data that are
20 amenable to evaluation. They referred early
21 on that this is being done in the context of
22 the IPCS mode of action, human relevance

1 framework, and the Agency's guidelines, which
2 describe a key event as an empirically
3 observable precursor step that is itself a
4 necessary element of the mode of action or
5 biologically-based marker for such an element.
6 Meaning you have empirically generated data
7 that can be modeled or evaluated in some way.

8 So I would submit in this
9 particular, given the apparent importance of
10 this chemical and all of the effort that's
11 been put into its risk assessment, that it's
12 time to do a benchmark dose analysis for
13 everything on this particular chemical, and
14 you're beyond the point where you can just
15 pick NOELs and do things.

16 So I would submit that at this
17 point in time one should be doing BMD analysis
18 on every key event, both sides of this new
19 picture, older picture and newer picture, HPG
20 and HPA. Obviously modeling it to the same
21 value, what do you use BMDL, BMD10, whatever
22 it is, and then compare as you do in the

1 cumulative risk assessment. And from that,
2 that will inform you which one among those
3 data sets, if any, should be the appropriate
4 ones from which to define points of departure
5 and proceed with the risk assessment.

6 One point that's probably more
7 related to our PK folks' comments is that it's
8 been pointed out several times, and I'm
9 looking particularly at the NHEERL data with
10 the parent and the metabolites, that not all
11 four of those substances necessarily do the
12 same thing when tested in the same system.
13 And, in fact, there are some examples where
14 the parent in one or two metabolites may exert
15 a particular effect and the other one doesn't
16 at all. There are a couple of studies that
17 have been pointed out. So how does one
18 account for that when trying to do the risk
19 assessment. I think one needs to be mindful
20 of that on the plus/minus examples.

21 So I'll leave it there and
22 delegate to somebody else to do be the sticky

1 for the moment.

2 DR. PORTIER: Well, before you
3 run, because as I was making notes, you made
4 a lot of references to key events, and I
5 wonder, in your mind, what are the key
6 elements, I guess is the word.

7 DR. FENNER-CRISP: The key -- no,
8 key events.

9 DR. PORTIER: Key events. What
10 are the key events in your mind that they
11 should be looking at, or what are the ones
12 that are going through your mind?

13 DR. FENNER-CRISP: Well, I'm not
14 disagreeing with the characterization for the
15 key events that previously were identified in
16 the early stages of the -- well, the mammary
17 tumor mode of action in the beginning stages
18 of looking at the repro and developmentally
19 effects.

20 So we've got -- I think there are
21 eight in there, but the last one referred to
22 the genotox thing, so it's essentially seven.

1 It's the precursor events plus the endpoint of
2 concern. If you don't have sufficient data to
3 do a dose response analysis for any one of
4 those, you know, it's got -- it's less
5 convincing than if you do.

6 And now and looking on the other
7 side of the -- the other axis, there are four
8 key events. So the question is, are there
9 empirically observable, quantitative measures
10 of those key events that could be looked at as
11 potential data sets for PoD identification.

12 DR. PORTIER: Okay. Dr. Reed.

13 DR. REED: Could I get a
14 clarification out of -- when you mention doing
15 benchmark dose analysis on every key event,
16 and -- were you thinking of treating each
17 benchmark response -- or benchmark dose with
18 the same benchmark response like whatever
19 percent of response, or would you be open to
20 a different interpretation in terms of the
21 significance of that response?

22 DR. FENNER-CRISP: Well, the most

1 useful thing would be to be able to model to
2 the same point so that you can make some
3 comparisons. But sometimes, depending upon
4 the nature of the data, one can't.

5 DR. REED: Okay.

6 DR. LOWIT: If I could just jump
7 in for a second there. I think in this
8 context there are two different but important
9 uses of the benchmark dose techniques.
10 There's -- I think the way that Penny's
11 thinking, in a more -- you do a mode of action
12 framework in a temporal concordance dose
13 response concordance analysis in the same way
14 that we've done for a couple of others, like
15 cadodylic acid I think is a good example,
16 where you take the data from the key events
17 and you select a common response level and you
18 evaluate all of the events at the same
19 response level to look at the pattern of the
20 sensitivity of those endpoints at one common
21 response.

22 But that's a different question of

1 using those data as a regulatory endpoint
2 because then I think you have to bring out a
3 more robust thinking of changes from
4 background or historical changes and the
5 relationship of the biological significance of
6 one key event to the other. So I think you
7 could use the benchmark dose differently in
8 that way.

9 DR. FENNER-CRISP: The reason I
10 offered that suggestion is that it is quite
11 possible and quite likely that the shape of
12 the does response for key event A may not be
13 identical to the dose response curve for B,
14 and looking at NOELs you may think they're in
15 this order, but modeling them they may shift
16 the order, and one has to take that into
17 consideration when moving to the risk
18 assessment.

19 DR. PORTIER: I guess the other
20 presenter is Dr. Krishnan.

21 DR. KRISHNAN: I'm going to be
22 pretty much repeating what I've said, but

1 let's see how much of it is the same and how
2 much is different.

3 Well, with respect to what
4 endpoints to base it on, we've heard a lot of
5 good discussion about the relevant endpoints
6 to be considered in the context of hazard
7 identification pretty much this morning. And
8 then, you know, based on considerations of
9 relevance and mode of action, you'll be
10 looking forward to as to which one of those
11 will go down the path of further analysis.

12 I see kind of two scenarios. I
13 think we already heard some of that. First
14 would be the PoD being derived on the basis of
15 key events, particularly as related to the
16 reproductive function and depicted by picture
17 3, as you alluded to. That's good as long as
18 it's the one MOA, or that set of MOA that
19 determines the critical outcome. And one MOA
20 may not fit all the critical out of a lot of
21 several endpoints we talked about.

22 So for some of the other

1 endpoints, I guess the alternative scenario
2 would be deriving PoDs based on the outcome
3 data itself and not necessarily based on the
4 key events being a part of the mode of action
5 framework that remains to be seen.

6 Technically I don't see us being
7 able to say which endpoints will have a lower
8 PoD, and that's unless these analyses are
9 actually done, because in part of kind of dose
10 measure that's used on the X-axis will also
11 determine -- and might change what one might
12 see as being sensitive or less sensitive based
13 on external dose only. There are examples to
14 that, in fact.

15 The development of PoDs based on
16 biomarker levels or perturbation levels would
17 be relevant as long as the relationship to the
18 functional outcome is established
19 quantitatively. You already heard some
20 response to that effect. So the PoDs are
21 based on, for example, hormone levels, so the
22 consideration of the homeostatic and

1 physiological considerations as a basis of
2 benchmark dose analysis would become important
3 rather than using the traditional 5 percent or
4 10 percent change, which was also kind of
5 unpolished, to induct in the comments before
6 me.

7 In this regard, one thing that I
8 thought would be nice to see varying
9 thicknesses of the arrows, you know, depicting
10 the proposed mode of action in Figure 3, or as
11 you go, as you move forward. In certain cases
12 the thicker arrow, that gives, you know, a
13 stronger weight of evidence whereas the other
14 ones could be weaker, it could be a dotted
15 line thing or it could be a solid, things like
16 that.

17 Or, in other words, for specific
18 toxicity perturbation based, you know,
19 analysis, it would be relevant to identify the
20 availability and competence of the data for
21 each of those critical events, for example,
22 from which the analysis could be done. So the

1 ideal -- the desired data would be one, but
2 what's available might be different. So
3 honoring them in terms of, you know, on the
4 basis of consideration of data availability
5 and their competence, the strength of the
6 relationship to the functional effect for any
7 of the key events that you would get in such
8 an analysis, and also the strength of the
9 model fit, which will be done at the end of
10 the BMD analysis, rather than just basing only
11 on the response modeling.

12 And in considering the PoD
13 derivations, I also think that it's important
14 to give due consideration to the internal dose
15 as the dose measure to replace the
16 administered dose given the fact that there's
17 some possibility of situations where you may
18 have some glutathione depletion or first pass
19 affects influencing the nature of the dose
20 response.

21 And in this regard, without
22 getting too much into the next question, I

1 think the measures of dose in deriving the PoD
2 will have to be somewhat related to the total
3 chlorinated forms, it appears, even though we
4 heard more about the two -- the metabolites,
5 the dealkylated ones that do not affect the
6 hormone levels, whereas some of the other
7 studies from Cooper, et al., that identified
8 the DACT, you know, in some evaluations of
9 both male reproductive functions. So I didn't
10 see the connection between the lack of effect
11 of DACT on the hormone levels, but effect on
12 the whole animal levels. So maybe we ought to
13 look at clarification on that aspect.

14 I just have a couple of sentences
15 to go through. Because in those studies there
16 were -- some atrazine-equal end doses were
17 provided for DACT, as for the other
18 metabolites, which then kind of, you know,
19 leads -- possibly leads us down the path of
20 atrazine-equivalent doses at dose measure, you
21 know, internally, which doesn't just represent
22 the atrazine but as well as the other forms,

1 and there's an equivalence that's derived.

2 I'm not saying that's appropriate, but it does
3 make sense to me when I went through those.

4 In that regard, PBPK models, might
5 be able to provide -- depending on the level
6 of the maturity, they could provide that kind
7 of an appropriate dose measure, because one of
8 the papers did present some of the total
9 chloral forms of the atrazine.

10 So the animal model in itself can
11 provide an improvement of the X-axis in
12 deriving, or getting a better handle on the
13 PoDs. And if there's a human model, that
14 means subsequently, you could, you know, even
15 think of replacing the interspecies factors.

16 So I'm not getting into the risk
17 assessment at all. I'll just stay -- pull
18 back. I'll erase the last word that said --
19 answering de facto. I'll leave it at that,
20 and if Cooper, et al., can clarify the
21 determination, the equivalences for DACT, I
22 would appreciate it, and whether they see a

1 connection or no between the hormone levels
2 and the hormonal effects.

3 DR. PORTIER: Dr. Cooper.

4 DR. COOPER: That's an interesting
5 question because -- I want to restate it just
6 to make sure I address it properly. If you
7 look at all the data with DACT versus the
8 other metabolites, and you look at the
9 reproductive axis, you look at the effects on
10 LH, we've done a pretty complete assessment in
11 the female on the LH surge with those four
12 different molecules.

13 And what we see, or what we have
14 seen over the years when we were naively
15 dosing equal amount of doses, you know, we
16 thought we were delivering the same number of
17 molecules or whatever, but when we eventually
18 went to look at the internal dose, and we were
19 fortunate enough in some of the more recent
20 studies to have assistance with looking at
21 different -- the four -- the three metabolites
22 plus atrazine in the blood, what found was

1 even though we were naively gavaging with
2 equimolar doses, we were getting considerably
3 different concentrations of the different
4 metabolites in the blood when we dosed.

5 And we've already addressed that,
6 very little atrazine, per se, at least in the
7 time points we looked at. We haven't done,
8 obviously, a complete series -- time series of
9 measurements.

10 But DACT was very high. That's
11 number one. So the internal dose of DACT is
12 very high whether we dose once or four times,
13 and given the DACT was really active, we were
14 sort of surprised that such high
15 concentrations were present. But secondly,
16 the amount of DACT necessary to inhibit the LH
17 surge was higher even yet. So now when we do
18 a dose response, and we don't have this
19 complete, but we have it piecemeal in
20 different studies, that we have an established
21 NOEL separately for DACT, we have some
22 preliminary data it might be around 100, which

1 is surprising or interesting because it's --
2 in itself, if you dose by itself, it still has
3 on the surge the same type of effect that you
4 see with atrazine, per se, or the other two
5 intermediate metabolites.

6 So my feeling is that that
7 particular metabolite, on the LH itself, is a
8 lot lower. And then if you go to -- but it's
9 still effective and I think that's the point,
10 the sticking point here. You know, in a
11 perfect world, you know, DACT, if you were
12 hypothesizing an adrenal involvement, it
13 shouldn't be active at all, and so on. So
14 that higher dose we see effects.

15 And then of course when you look
16 either in vitro, and this is the thing, it's
17 very interesting about the comparisons is that
18 when you look in vitro and the effects on
19 adrenal, then DACT seems to have very -- even
20 more minimal effects, if you will. So that's
21 the situation.

22 I think what we're dealing with

1 here of course is more than one -- like my
2 mother used to say, more than one way to skin
3 a cat, as that you can effect that surge
4 either directly using DACT, or with some of
5 the other compounds there may be a much
6 broader series of events that take place. So
7 even though it doesn't line itself up nice and
8 neatly, I think we're still dealing with
9 compounds that all eventually will knock down
10 the amount of luteinizing hormone secreted.

11 And did that get at what you're
12 after? In other words, I agree. Additionally
13 though, what I was more interested in was the
14 study of Laws 2003, which was on page 31 and
15 32 of the document.

16 DR. COOPER: Of the female?

17 DR. KRISHNAN: Yes. And for male
18 it was the Stoker 2005 --

19 DR. COOPER: Right. They both
20 were --

21 DR. KRISHNAN: -- on page 34.

22 DR. COOPER: -- in Stoker paper

1 she dosed again with 21 days in the male
2 which -- 31, I'm sorry, the female gets -- 31
3 days, that's a month of dosing, daily dosing,
4 so again, even though in that one we had a
5 LOEL th was down in the range of the other
6 metabolites. I think 30 days of dosing is
7 different than the comparisons that I was
8 making with the shorter term.

9 And, Susan, the female, the NOEL
10 for DACT, did you get a NOEL in the female for
11 DACT in the pubertal? I know you compared
12 propazine and one of the other intermediate
13 ones, but not -- she's frantically -- I can
14 tell frantically searching through her
15 document and saying that DACT was also
16 examined and she found that DACT --

17 DR. PORTIER: Let her speak for
18 herself.

19 DR. COOPER: -- was delayed
20 vaginal opening in these animals at a dose
21 of --

22 DR. LAWS: I've got --

1 DR. PORTIER: Identify yourself.

2 DR. LAWS: Susan Laws, EPA, and
3 the no effect level for DACT was 16.7
4 milligrams, which was equivalent -- equimolar
5 at the time to atrazine 25. That was the no
6 effect. So probably the LOEL was 50 for DACT.

7 But one for the things that I
8 wanted to mention, in the 2009 papers,
9 although in Laws, et al., it's one dose,
10 but -- and that, in Tables 4 and 5, we had the
11 plasma levels of the parent compound and the
12 metabolites on their dose of atrazine. And
13 that's what Ralph was mentioning early -- and
14 we also have -- when we treated the animals
15 with DIA or DACT, and we see that in the first
16 we have a dose -- I mean a time course from
17 five minutes to three hours, and you can see
18 the progression of atrazine is essentially the
19 same in vivo, and then the progression to the
20 increased amount of DACT.

21 And in Fraites, et al., she doses
22 four days and she saw that DACT was --

1 continued to accumulate. So it may be in the
2 pubertals that DACT does continue to
3 accumulate some in the plasma, which may
4 actually get to a point where it's causing
5 these effects, because the pubertals are a 21-
6 or a 30-day exposure period versus the acute
7 things.

8 DR. PORTIER: So I think what --
9 Dr. Reed wants to open it up now for anyone
10 else to discuss endpoint. Anyone else? Yes,
11 Dr. Greenwood.

12 DR. GREENWOOD: I just wondered if
13 I could ask a point of clarification. When
14 you looked at the accumulation of diamino
15 chlorotriazine in the plasma, was it free or
16 bound, because if it's bound to the serum
17 albumin covalently, it's not going to be doing
18 a lot metabolically.

19 DR. LAWS: I'm sorry. This was in
20 the plasma, and it's total -- as far as I
21 know, it's in plasma, not serum.

22 DR. PORTIER: Dr. Horton.

1 DR. HORTON: I have a question
2 about the definition of a key event, or maybe
3 I just misheard something between what Dr.
4 Fenner-Crisp and what Dr. Krishnan were
5 saying, because what I understood from what
6 Dr. Fenner-Crisp was saying was that a key
7 event has to be part of the MOA, but what I
8 thought I heard Dr. Krishnan saying was that
9 in looking for points of departures, that some
10 of the key events may not belong to the
11 current mode of action.

12 Were you saying that, while we may
13 see some key events that, you know, aren't
14 necessarily part of a mode of action, or were
15 you simply referring to the breast cancer, or
16 the mammary tumor mode of action, but they may
17 be part of the new mode of action that's the
18 model on page 3? Or what did you actually
19 mean?

20 DR. KRISHNAN: Okay. In terms of
21 the mode of action framework, the picture 3,
22 what I indicated was maybe there are some

1 connections and lines that are -- that could
2 be strengthened and some that can be weakened
3 rather than considering all of them as being
4 equally, you know, supported by the current
5 data, that something they thought could be
6 then.

7 On the other hand, for specific
8 endpoints that are used in assessments, a
9 single mode is not going to -- a single mode
10 of action framework might not end up
11 explaining all of the endpoints and outcomes
12 for which, you know, you're going to base the
13 assessment on. So, you know, it's not like,
14 you know, going through the same mode, the
15 house, and then a lot of the outcomes come
16 through, that probably is not a realistic --
17 and so in that case --

18 DR. HORTON: Okay.

19 DR. KRISHNAN: -- they might do
20 some analysis even without going through the
21 detailed mode of action if they don't have --

22 DR. HORTON: Okay. Dr. Horton

1 again. So in this case now the house has some
2 out buildings, we have a barn and -- okay.

3 DR. PORTIER: And I was -- I've
4 been following that, I'm wondering what you
5 think some of those out buildings might look
6 like, because we've been talking about kind of
7 non-hormonal process, repo/developmental
8 events that are neuro or whatever.

9 DR. HORTON: Okay. In that
10 context, the neuro effects that we were
11 talking about are just in the attic because
12 they're on top of the regulatory system that's
13 part of the HPG/HPA system. And so they are
14 built on top of the regulation of the
15 reproductive and the adrenal system because
16 they are part of the system that regulates
17 that, in the hypothalamus and limbic system.

18 DR. PORTIER: One question. Is it
19 possible to draw a picture of that? I mean or
20 add to the -- add to Figure 2 to really
21 explain what you're trying to get at.

22 DR. HORTON: I can do that.

1 DR. PORTIER: I just -- I'm a
2 visual guy.

3 Yes, Dr. Fenner-Crisp.

4 DR. FENNER-CRISP: Maybe another
5 thing that would clarify what Dr. Krishnan
6 said was, not only might you select from the
7 key events related to the mode or modes of
8 action that have been postulated for
9 reproductive and developmental effects, you
10 may also, by virtue of time and exposure
11 duration choose to select a totally different
12 outcome for which no mode of action analysis
13 has been developed to this point in time.

14 And if you look at the body of
15 data related to this chemical or any other
16 pesticide, there are whole lot of other things
17 that get measured in apical studies for which
18 mode of action analysis may never get
19 developed, like body weight changes in a
20 chronic study, or things like that.

21 So it may be appropriate to go to
22 some of these other data sets by virtue of

1 subpopulation, duration of exposure, et
2 cetera, et cetera, and use that data set as
3 the basis for your point of departure. And
4 you can use any of the stuff we've been
5 mulling over for the last two days.

6 DR. PORTIER: This is Ken Portier.
7 But my understanding is that probably was
8 looked at in the 2003 risk assessment, and
9 ruled out in favor of the LH surge --

10 DR. FENNER-CRISP: Except that I
11 offer the admonish that there may be things
12 known about some of these other endpoints now
13 that weren't known back then that you may want
14 to take a second look at.

15 DR. PORTIER: Dr. Lowit.

16 DR. LOWIT: With the caveat of
17 what Penny just slapped us on the wrist about,
18 I think at this point we have a little bit of
19 confidence -- I don't want to go too far --
20 that the precursor events around the hormonal
21 changes are more sensitive than the functional
22 outcomes. I'm not aware of any of the

1 functional outcomes that are more sensitive
2 than are the hormonal changes. And someone
3 kick me if I'm wrong. There are a lot of
4 people behind me that probably know the data.

5 Ralph's arguing yes, so may I --
6 that's part of what we'll ask ourselves, but
7 I think our driving theory right now, and
8 there's -- we haven't seen anything to get off
9 that train, but if we see something, we will,
10 is that the hormone changes, or the precursor
11 events will be -- we expect them to be more
12 sensitive than the outcome data.

13 DR. PORTIER: Dr. Akana I think
14 was next. And then Dr. Hayton.

15 DR. AKANA: Okay. I'm not
16 positive I've got a grip on the idea, but I'm
17 going to throw out an endpoint, and it's just
18 a theoretical possibility. And that is
19 actually continuous recording of body core
20 temperature. Now normally you think, okay,
21 core temperature, you know, it's core, it
22 doesn't move that much, but actually with the

1 nice little implantable transponders, you can
2 demonstrate beautiful basal circadian rhythms
3 in temperature, which are reproducible.

4 The stats people will love it. It
5 generates hundreds and thousands of points for
6 you. It's got maxima and minima, it can be
7 modeled, it's sensitive to glucocorticoids,
8 it's sensitive to food intake. I don't know
9 the data in females, but I'm hoping it shows
10 beautiful cycles you can follow through. One
11 of the beauties is that you can give -- you
12 know, once the animal recovers, you can give
13 your acute dose and keep continuing, and
14 you're collecting online data.

15 So it's not so great for the
16 immune measures that mostly would catch
17 accrued temperature, but I'm wondering how
18 many people could be happy with that kind of
19 endpoint. Oh, and then it covers catechols.

20 DR. HAYTON: Yes, Bill Hayton.

21 DR. LOWIT: One more quick -- with
22 quite a number of these you'd catch locomotor

1 activity which you can, from the same
2 transmitters, so that can be -- usually home
3 cage is really valuable, or depending on your
4 model it could be other locomotor measures,
5 which also have -- can be verified with photo
6 detectors.

7 DR. COOPER: So let me ask you the
8 question then, if you did this and we have the
9 radiotelemetry and it's accessible to us, how
10 readily accessible, I'm not sure of, and
11 there's some of my colleagues who are looking
12 into some of these approaches, but we have --
13 I could envision three outcomes, and I'll run
14 them by you and you'll see the dilemma that
15 you're suggesting.

16 The first outcome would be we see
17 a difference, and we see at just about the
18 same dose response that we see -- I'll pick
19 another endpoint, the surge, okay. So we've
20 talked about that. How do I establish a
21 functional link on that one?

22 I mean this is really what we're

1 getting at a little bit. You've got another
2 endpoint that changed. Okay. Granted. And
3 it's a measure one, a repeated one. But we
4 have to establish a functional link. And
5 there's the literature there, I'm sure,
6 there's a literature on everything.

7 But the other one is it comes in
8 at a lower dose. How confident can we be that
9 that's indicative of an adverse outcome
10 functionally linked to delayed vaginal opening
11 or mammary gland tumor development and so on?
12 And then the third one is no difference, I
13 guess, or high dose difference because I doubt
14 that you'll see that if we get involved with
15 any of these measures you can be pretty sure
16 you'll see effects.

17 So I mean the question that we
18 really have to get at is, with what we have
19 now, how can we proceed in terms of taking the
20 best estimate of what the real predictors of
21 adverse outcomes are in the data sets we have?
22 In the previous SAP they agreed that the surge

1 itself was a good key event that could be used
2 at this. We were concerned that the adrenals
3 may offer additional lower doses or something
4 like that.

5 But I would doubt -- if we took
6 Penny's approach, I don't think we'd see a
7 difference in the benchmark because I think
8 they'd probably be pretty -- between the, say,
9 the surge and the ACTH or cort or whatever --
10 however you want to evaluate that.

11 So, again, I think we're really
12 interested in your comments on which is the
13 better of what we've got right now knowing
14 that we don't have the Cadillac we'd love to
15 have.

16 DR. PORTIER: Dr. Hayton.

17 DR. HAYTON: Thank you. I just --
18 I'm still puzzled. The question, 1.9, what
19 would be appropriate endpoints to consider.
20 I've been trying to write something down here,
21 and I don't think I've quite heard it yet, but
22 it -- we're talking about HPA/HPG signals.

1 Right? Okay. And then downstream sequelae to
2 those particular signals. Okay. Thank you.

3 DR. PORTIER: So I think the LH
4 surge is still in there. Right? And there's
5 some others on the HPA axis that are going to
6 come up that we're looking at. And the
7 question is, is there anything beyond that
8 that's in that part of the box. Right? And,
9 Dr. Horton.

10 DR. HORTON: Okay. Two things.
11 One is I think we need to redraw the figure to
12 be able to figure out what some of those key
13 events may be to ask what the endpoints are,
14 because I think that's what you want to know,
15 is what are those endpoints, and those
16 endpoints have to be defined by looking at
17 that box.

18 And with respect to the functional
19 issue of the rhythms data, how you interpret
20 that functional outcome will depend on
21 specifically what characteristics of the
22 rhythms are disrupted and how they changed,

1 because if it's increased activity, you've got
2 one functional outcome; if it's decreased,
3 it's a different issue; if it's a delay in the
4 rhythm, as I've heard some suggestion that
5 there's a delay in the onset of the rise, that
6 means a different thing. So there is actually
7 a lot in terms of the functionality that can
8 be interpreted from looking at changes in
9 circadian rhythms. And those things do have
10 a great deal of impact in terms of looking at
11 metabolism and health outcomes.

12 DR. PORTIER: But what I keep
13 hearing is that the early endocrine things,
14 like LH surge, are going to be precursors to
15 any of those functional -- if you look at
16 Figure 3, the functional -- or further down
17 the line, and I think the argument is that
18 there's going to be less sensitivity to that
19 and to these things that are in the pituitary
20 box --

21 DR. HORTON: Well, it's --

22 DR. PORTIER: -- or in the CNS

1 box.

2 DR. HORTON: Yes, except that you
3 can pick up -- no, you can pick up circadian
4 changes in males but you can't -- you're not
5 going to get an LH surge in females, and so
6 therefore if you're concerned about reducing
7 animal care costs and use of animals, you can
8 look in both males and females. The advantage
9 of looking in males is you don't have to worry
10 about a four-day cycle, so you've reduced by
11 a factor of four the number of animals that
12 you're working with.

13 So -- although you do have to deal
14 with some of these issues that seem to be
15 sexually differentiated. And also you can
16 look at different ages. And so you do have
17 some different considerations to take in mind
18 whether you're looking at a circadian marker
19 rather than an endocrine marker.

20 DR. LOWIT: I think there's just
21 one point that I'd like to make before we sort
22 of keep moving, is that what's unique about

1 Question 1.9, that's different from 1.2 up to
2 1.8 is that if you go back from a few days
3 ago, the rubber meets the road analogy, this
4 is where the rubber meets the road, and the
5 Agency has to start making some choices soon.
6 Soon, you know.

7 And so to the extent that we
8 can -- you can, in your mind, as hard as it
9 may be, separate yourself, put yourself in our
10 shoes for a minute, that the Agency has to
11 make some choices very, very soon, before
12 September, in fact. So between -- in the next
13 four months.

14 So the things that we have in
15 front of us, that you have, and the seven to
16 ten things that Liz listed up on her slides a
17 few days ago, are all there is to make those
18 choices from. Okay. With respect to these
19 non-cancer endpoints. And so this is a
20 science question because it's getting at the
21 things to think about as we make those
22 choices, but this is not a research open-ended

1 kind of question.

2 DR. PORTIER: Dr. Fenner-Crisp,
3 and then Dr. --

4 DR. FENNER-CRISP: Yes, Dr.
5 Krishnan referred to it. One thing that
6 currently doesn't exist, that I'm certain will
7 before you make your decisions, that would
8 have been -- that would be very helpful to
9 have, is the framework analysis prepared in
10 parallel to that which was done for the
11 mammary tumor mode of action. And then one
12 could -- it would speak to all the things that
13 were talked about: about how thick the arrows
14 ought to be from where and where, what's the
15 credibility of the data set, you know, and all
16 of those kinds of things, the temporal
17 relationships, the dose -- you know, all that
18 stuff.

19 Were that to exist, it would be
20 much easier for this panel to answer your
21 question. And I know you will be preparing
22 it.

1 (Laughter.)

2 DR. LOWIT: Thank you. Yes.

3 Absolutely. Probably starting next week
4 actually.

5 DR. FENNER-CRISP: Yes.

6 DR. LOWIT: Our assay is halfway
7 done. All right. But some of the studies
8 that Cooper and company and Syngenta are doing
9 are important in that because they provide
10 some of the causal links, and some of the
11 Handa data from the other day really
12 establishes some causality, and there's a
13 number of dose response studies in there that
14 are driving the doses five and below, which
15 gets out some of the comments.

16 So it was really almost impossible
17 to do a few months ago, but three months from
18 how we'll actually be a lot --

19 DR. FENNER-CRISP: Well, I
20 appreciate that, and I wouldn't wish to
21 suggest I had an expectation it would exist
22 yet. But the point is that eventually, before

1 you make a final decision, you have to have
2 created that document in order to best present
3 the argument for selecting the things that you
4 select. That's all I'm saying.

5 DR. LOWIT: Yes. And Dr. Portier,
6 I think, speaking for the team, at least in
7 this first part, I think we've heard what
8 we've sort of expected or thought, and I don't
9 want to beat it to death. I think the really
10 interesting part is the second part.

11 DR. PORTIER: I was going to
12 acknowledge Dr. Reed, and then ask her to
13 summarize so we can move on to the second
14 part.

15 DR. REED: That was pretty much
16 why I'd raised my hand. I think we heard
17 enough to move forward. There's certain
18 things that we wouldn't know until, you know,
19 you get into the analysis, and so that's my --

20 DR. PORTIER: So let's pop up the
21 second part of the question, and I'll turn to
22 Dr. Krishnan to talk about the issue of

1 duration. Right? And some of the PK issues.

2 DR. KRISHNAN: I'm not going to
3 make it interesting, if that's what you're
4 looking for.

5 (Laughter.)

6 DR. KRISHNAN: But I have some
7 able colleagues by my side who might try that.
8 I'll put in some of my thinking, and then I'll
9 leave it up to the colleagues, and then I'll
10 come back with additional comments.

11 The question essentially relates
12 the duration of toxicological concern and the
13 frequency of drinking water monitoring that
14 we've been talking about on and off, you know,
15 at least yesterday. And in defining the
16 exposure window of interest requested, that's
17 the comment on the pharmacokinetic dynamic
18 considerations with respect to the atrazine
19 effects on the HPA screening axis.

20 I think initially as we think
21 about the problem in terms of acute versus
22 chronic, or repeated exposures, you can

1 always, you know, somewhere draw the line of
2 intermediate versus chronic, because often the
3 continued exposures get us to what is called
4 as a steady state. So knowing this
5 characteristic of this chemical, I don't
6 expect to -- at least kinetically I don't
7 expect to see differences between intermediate
8 versus chronic duration.

9 So if we consider acute versus
10 chronic scenarios, normally when we protect
11 against chronic effects, protection against
12 acute effects is automatic, and the vice versa
13 is not true. So then we also saw some of the
14 box and whisker plots that showed increasing
15 space as you went from chronic to acute.

16 I'm not going into any specifics
17 of the effects, critical effects between acute
18 and chronic, but in general terms for acute
19 effects you tend to think of maximal
20 concentration as the driver, maximal
21 concentration internally, not in the plasma or
22 the critical tissue. So it's a question of

1 whether we exceed a threshold maximal
2 concentration, for a C-max, and for how long.
3 That's the question with respect to acute
4 scenarios.

5 Then for repeated exposures of
6 chronic, it's often the inner greater internal
7 exposure, or the average daily exposure.
8 That's usually a useful measure. Those are
9 some for the generalities, even though you can
10 always come up with exceptions.

11 Now, when we think about the
12 frequency for drinking water monitoring and
13 the plots of the water concentrations that we
14 saw, you know, there's peak who appeared for
15 a day or a shorter duration and there was some
16 trials and so on mixed with it.

17 But relating that, or viewing that
18 in the context of toxicological concern
19 requires that we think of the continuum of
20 events, meaning that from the water
21 concentration that we see was on the pictures,
22 the next one that I would think of is the

1 exposure pattern, what is the rate and route
2 of contact. Now it might take just a half a
3 cup of water versus a bottle of water. That's
4 a factor of 10, and then you're talking about
5 the peak and then another -- or differences
6 there.

7 So the exposure -- the rate of
8 uptake and then the route of exposure, whether
9 it's only oral, or dermal and other routes,
10 whether they're relevant or not. In most
11 drinking water scenarios, those are
12 considered. I'm not -- it seems to me that
13 the dermal absorption is much less, but I'm
14 unable to give an quantitative estimate based
15 on permeability coefficient. I don't know if
16 I missed the permeability coefficient. I
17 haven't seen it, but those can be estimated.
18 EPA has some methodologies available.

19 So from there, the exposure
20 pattern, or the uptake pattern, and then we to
21 consider the pharmacokinetics which is the
22 ADME, the initial step of rate of absorption

1 would appear to be the limiting factor, while
2 it's relatively a lower rate of absorption as
3 it seems from some of the papers we have seen.

4 So depending on the quantity and
5 the frequency we take, there's the rate of
6 absorption that takes into -- that gets into
7 the play. That's one of the reasons why I
8 feel that an integrated measure of exposure
9 would be more useful rather than concentrating
10 on any of the individual peaks and trials.

11 And also when you, you know, integrate and use
12 an AUC for -- in this context, either
13 internally or externally, the area under the
14 curve of concentration versus time, that also
15 deletes out any -- possibly deletes out any
16 impacts or concerns about specific peaks, or
17 very sharp duration.

18 Also, we heard some -- in terms of
19 the pharmacodynamics aspects, I have done the
20 environmental concentration, the uptake,
21 pharmacokinetics, even though I haven't gotten
22 into all of the details, which my colleagues

1 will, and then in terms of the
2 pharmacodynamics as well. And Dr. O'Byrne
3 talked about it this morning. I thought you
4 emphasized the importance of the sustained
5 chronic alteration of the precursor levels,
6 especially when you talked about the cortical
7 levels this morning. That's what really
8 determines the impact on the LH surge, if I
9 didn't actually put it.

10 So in total, considering the
11 continuum of those events, I'm coming back to
12 the question of duration of the tox concern
13 versus the frequency of monitoring. My
14 initial take -- even though I can learn from
15 people and change my mind later on, my take is
16 that, you know, monitoring the way we have
17 seen, like a weekly monitoring interval over
18 a three-month period, or a certain period, I
19 think will serve the purpose.

20 Since we haven't seen, or at least
21 I haven't seen a study where it really strikes
22 by saying that while the critical window of

1 exposure is one day, or between day 3 and day
2 4 of -- during a gestation period or
3 something, then it really puts you under the
4 pressure to have to essentially monitor within
5 that kind of a time frame all the time,
6 because you don't know who will be in that
7 time frame and when.

8 Since that doesn't seem to be the
9 case, it appears to me that the area under the
10 curve kind of approach would be sufficient at
11 these intervals, and the Agency's may not be
12 as sensitive to very short term fluctuations.
13 And at some point, some kind of sensitivity
14 analysis might be of use. Now once we do
15 determine a PoD, we already have the dose
16 measure, you can always relate that to
17 essentially water concentrations to these
18 temps.

19 And I've tried to ask the question
20 of what is the most sensitive parameter that
21 really drives my, you know, dose measure that
22 I'm using in a risk assessment, or in a dose

1 response curve for humans. Is it the uptake,
2 my peak, and so forth? So that would also
3 give some -- well, I think will give some
4 added confidence in terms of use of, you know,
5 the area under the curve kind for a measure,
6 even for the environmental concentrations.

7 I think with that I'm going to
8 yield the rest of my time to Dr. Greenwood
9 from the County of Portsmouth in the UK.

10 DR. GREENWOOD: Okay. I just want
11 to address, because I'm sure everybody's read
12 what's in the white paper, but I just want to
13 address what I think are one or two important
14 points that hit me between the eyes when I was
15 reading some of these papers.

16 One of the things that came up was
17 that in rats we get this binding to hemoglobin
18 and to plasma proteins. So if you're looking
19 at -- want to look at the level of free
20 diamino chlorotriazine, because this is the
21 stuff that binds rather than the other
22 metabolites, or atrazine to any great extent,

1 then it's certainly going to have an
2 influence, or should have an influence on the
3 interpretation of the levels that you're
4 measuring in blood.

5 And some of the other studies sort
6 of acknowledge that this happens, and then
7 forgotten about it when they come to interpret
8 the profiles, particularly if you're trying to
9 get a handle on what is a critical exposure of
10 site of action to a particular toxicant,
11 whether it be atrazine or one of the
12 metabolites. And it just seemed that when you
13 look at some of these profiles, that in some
14 of these studies, because they're high dose
15 maybe, I don't know, but because they're high
16 dose we're getting really not very much
17 relatively of the glutathione derivatives
18 which are relatively -- seem to
19 pharmacologically inactive, as you might
20 expect, were compared with the oxidative
21 metabolites of atrazine and atrazine itself.

22 And certainly the diamino

1 chlorotriazine seems to be present in some of
2 these studies at about a factor of 100, more
3 than any of the other metabolites. It really
4 is, after something like 12 hours, is the
5 predominant metabolite. Atrazine seems to be
6 peaking after a very few hours. So this just
7 seemed to be the major metabolite.

8 And what's more, when people
9 started to dose this on its own rather than
10 atrazine just to follow the kinetics of it,
11 it's got a very rapid absorption, and a lower
12 level of elimination. It's got a text book
13 sort of profile for that sort of compound.
14 And it does seem to bind -- because it binds
15 to cysteine, it does seem to expose cysteines.
16 It binds to a wide range of proteins.

17 Now, obviously there's a large
18 volume of albumin in the bolus, predominant --
19 in the plasma it's the predominant protein and
20 it does bind to one particular cysteine in
21 there. But it also seems to bind, when we
22 flip to the later studies, to a lot of

1 different proteins in, for instance, the
2 pituitary. But, again, there's absolutely --
3 I have no idea what the toxicological
4 significance of that might be, and how much of
5 the -- like how much of that protein is
6 removed, how quickly it's replaced, if it's
7 just -- is it detected as being non-functional
8 and does it replace. I don't know.

9 So it could be an important
10 factor, not just for the pharmacokinetics, but
11 maybe for -- it appears that this stuff is
12 inside certain tissues, but if it's found in
13 there, then it's not available. But is the
14 binding itself toxicologically significant.
15 And I don't think at the moment anybody has
16 any idea.

17 So I think this diamino
18 chlorotriazine is really something that can't
19 be discounted, mainly because it's in there in
20 such large quantities and because it does bind
21 covalently to any cysteine that's in the right
22 sort of conformation.

1 I think the other things that came
2 across to me, there's a study by Carroll, et
3 al., where they've compared the human and rat,
4 gut and uptake of it, and it did show that
5 the -- I think I said earlier that the
6 absorption is very similar in the two.
7 There's quite a high correlation coefficient,
8 in fact, a coefficient determination of .8.
9 But between the bioavailabilities because of
10 this difference in metabolism in the gut, they
11 R squared value goes down to about .3.

12 So it's -- it think there are
13 species differences, and although you might
14 predict in terms of absorption what goes on,
15 and you'd probably be fairly reasonably
16 accurate going from one species to another, in
17 terms of bioavailability you may be a long way
18 out, and it's the bioavailability of course
19 that's the most important thing that we need
20 to look at. It's no use something being
21 absorbed if it then gets wiped out in the
22 first pass of metabolism.

1 So I think, again, looking at some
2 of the studies, some of the models were
3 dismissed because there weren't data to test
4 them and so on, but I think that the model
5 fitting process gives us some take home
6 lessons, I think, about what are the more
7 sensitive parameters in the model and gives us
8 some idea of what would make a big difference.
9 And in most cases, what seems to make a big
10 difference to the exposure is this metabolism,
11 either in the -- by entry sites or by the
12 liver in the first pass of metabolism.

13 And that's why where we -- when I
14 was asked earlier about implants where you
15 avoid some of that metabolism, I mean
16 eventually it's going to meet those same
17 things because the gut gets a blood supply, it
18 doesn't just have a blood supply taken away to
19 the hepatic portal vein, it also needs an
20 arterial blood supply. All of the tissues
21 come in contact -- once it's in the blood
22 stream, every tissue in the body comes in

1 contact with it, target tissues and non-target
2 tissues.

3 So, again, I think some of these
4 issues need looking at because I think what's
5 important is, when you're looking at trying to
6 get a dose response curve, is what is
7 available, what is available for interaction
8 with the site of action, because if it's bound
9 up somewhere, it's not available, it's
10 covalently bound to an albumin.

11 I think I'll leave that there. I
12 think those were the main points that, when
13 people are looking for dose response
14 relationships, they may not always see one,
15 and it could be because you get differential
16 metabolism and you get different
17 pharmacokinetics at high doses and at low
18 doses. And I think one of the other panel
19 members may have something to add to that, so
20 I'll leave it there.

21 DR. HAYTON: Bill Hayton. Just a
22 few comments to summarize my report I'm going

1 to turn in. The first thing is that after
2 oral gavage, that the -- in terms of kinetics,
3 the hormonal perturbation occurs very quickly
4 after atrazine administration. I think it's
5 the Fraites papers shows within in 15 minutes.
6 Even though it's a fairly large dose of
7 atrazine, we know from McMullin's study of
8 kinetics, that probably most of the dose is
9 still in the GI tract, so it seems like it
10 doesn't take all that much atrazine hitting
11 the pre-systemic metabolism machinery and then
12 whatever goes on into the systemic
13 circulation. Right away it triggers hormonal
14 perturbations in the HPA axis.

15 I think another thing that's
16 important about the kinetics is that atrazine
17 and its metabolites are not persistent. They
18 seem to be eliminated fairly quickly. There
19 aren't really good estimates in the rat of
20 half-life of the individuals species, I didn't
21 think, reading the PK papers. But just
22 looking at the overall half-life of

1 radioactivity, something on the order of about
2 10 hours in the rat, if you scale that to a
3 human maybe 24 hours, it would be three- to
4 four-fold longer typically.

5 Anyway, what this means is if you
6 stop -- if a person is exposed to atrazine in
7 drinking water, you get rapid onset of effect
8 on the HPA axis. If you stop administration
9 the effects -- it seems like the direct
10 effects have to go away fairly quickly because
11 of the relatively short half-life.

12 So those are some of the things
13 that I think that we know. If we ask the
14 question what's the lower limit of magnitude
15 and duration of perturbation of that hormone
16 signal that produces functional outcome
17 disturbance, in other words if you say that
18 the signal is just a precursor to a functional
19 outcome, adverse event, I don't think that's
20 been characterized. I don't think we know,
21 you know, how much perturbation of this signal
22 and/or for how long.

1 And this was a question I asked
2 Dr. O'Byrne this morning about, you know, the
3 acute versus the chronic and I think the
4 answer was it's the more chronic exposure is
5 probably the more relevant exposure. But I
6 think that's something we don't know.

7 And then finally, I think the
8 exposure window of interest is not readily
9 definable with the data we have now. Acute
10 perturbation seem to be less relevant than
11 chronic perturbation, and I think without the
12 signal functional outcome relationship being
13 well defined, it seems prudent just to use the
14 lowest observed adverse effect level that
15 perturbs biosignal as the point of departure,
16 or as the endpoint to define that.

17 DR. PORTIER: Dr. Greenwood.

18 DR. GREENWOOD: I'll just pick up
19 on one point. And it's difficult to get a
20 feel from these studies which are using oral
21 gavage because of what Dr. Hayton just said,
22 that a lot of the dose is still actually tied

1 up with the bolus and it comes out slowly,
2 probably in the intestine, over a period of
3 time. I think the whole dose eventually will
4 be absorbed, but -- or most of it, but it's
5 very difficult to try and get a feel for what
6 would be the pharmacokinetics if it was in the
7 drinking water.

8 And the problem is that, you know,
9 if you start thinking about taking in lower
10 levels in the drinking water, then you've got
11 to detect it, and if you dilute that by all
12 the tissues in the body, then you've problems
13 in the detection. And that's a real problem.
14 So it's very difficult to see how you get a
15 more realistic model of drinking water intake
16 because of these problems of level of
17 detection.

18 But at some time -- conceptually I
19 find it difficult to go from what's going on
20 with oral gavage and what would be going on
21 with intake throughout the day at lower levels
22 in drinking water. And I think, you know,

1 you'd probably get a different picture in
2 terms of metabolites and everything else.

3 DR. PORTIER: Dr. Schlenk.

4 DR. SCHLENK: Yes, this is very
5 interesting reading. In terms of the
6 kinetics, I think, particularly since most of
7 the doses are all fairly high dose experiments
8 that are primarily oral, and I think it really
9 lends itself to a PK -- PBPK sort of analysis,
10 I think it's perfect because I think,
11 particularly from the metabolism side, you
12 could argue that there's tremendous
13 differences between high dose oral exposures
14 and low level chronic exposures, just from a
15 KM perspective in terms of
16 the P450s that are involved in metabolism.

17 One thing I would note before I
18 forget, actually I wrote it down, if for the
19 non-cancer endpoints that are going to
20 evaluated for this fall, I assume you're going
21 to have a smoking history on some of the
22 individuals for that. I think that would be

1 a very important endpoint since 1A1 seems to
2 be a fairly important metabolizing enzyme for
3 atrazine. So I think that's going to be
4 obviously induced in smokers, that's going to
5 be a real, I think a real important sort of
6 issue related to that. So I assume that
7 information will be known in terms of that.

8 But to get to Dr. Greenwood's
9 comparison of the human and the rat, there
10 actually is quite a bit known in terms of
11 metabolism of atrazine in terms of its profile
12 in P450 structure. And those data are
13 actually fairly well characterized between
14 humans and rats, so consequently those data
15 should be readily available for PK analysis in
16 terms of uptake, particularly with low level
17 exposures, because, just to give you an
18 example, if you are giving an oral bolus dose,
19 which we've sort of been hearing about, the
20 P450s that metabolize are going to be
21 completely different because in that sense,
22 again I mentioned this earlier, you're CYP3As

1 are actually going to be more appropriate
2 because they're high KM-based P450s.

3 So consequently your profile is
4 going to be different, and since those are a
5 little bit higher -- more highly expressed in
6 the GI you might not ever see atrazine
7 actually be absorbed to a certain degree in
8 that sense. However, at low level doses, then
9 a different P450 profile takes place. And,
10 again, that's 1A1, which happens to have a
11 higher KM -- I'm sorry, lower KM, higher
12 affinity for atrazine.

13 So, again, I think those
14 differences alone will change plasma
15 concentrations, which when -- eventually will
16 change target organ concentrations in terms of
17 your model. I don't think any of that had
18 been sort of evaluated, at least in the
19 literature that I was provided.

20 So I think those are sort of
21 critical issues in terms of metabolism, and
22 particularly since it seems the metabolites

1 tend to be not as potent in terms of its
2 interaction than the parent compound. So I
3 think figuring out those sort of issues
4 related to the metabolism, at the gut, the
5 level for the gut, as well as the liver, are
6 critical. And then, again, knowing what we do
7 know, the difference between the rat and the
8 human, you should be able to extrapolate that
9 pretty readily, I would think, between those
10 two.

11 DR. PORTIER: Dr. Chambers.

12 DR. CHAMBERS: I think all of
13 these comments have been extremely
14 interesting, and I guess I have the mind set
15 of something that's probably a food
16 contaminant, you're going to get it all as one
17 contaminated apple or something like that.
18 And when Kannan was talking I got to thinking
19 that with the two liters of water that
20 everybody drinks every day, that's distributed
21 pretty well throughout the day as opposed to
22 one big slug.

1 And so the -- I guess again the PK
2 considerations need to be done of getting that
3 dose over an extended period of time during
4 the day, and it's not going to be comparable
5 very well at all, I don't think, with some of
6 these gavage studies that you're having to
7 compare the endpoints with.

8 So just keeping all these points
9 into consideration as you do your analysis
10 over the next few months and do the
11 consideration I guess tomorrow on the drinking
12 water frequency and all, a very different
13 exposure pattern with drinking water as
14 opposed to the gavage type studies in the
15 animals.

16 DR. PORTIER: Dr. Reed.

17 DR. REED: Yes, as we're talking
18 about PK I was thinking that it's also
19 important what is the dose metrics that you're
20 going to be using to compare the rats and
21 humans for the endpoints of concern. And I'm
22 hearing in some cases area under the curve, in

1 some cases might be peak, and so it might be,
2 you know, more or less related to the
3 endpoints that you are trying to characterize.

4 And, you know, according to
5 Penny's suggestion that we do endpoints based
6 on the schematic of things for the mode of
7 action, and it might be different from one
8 step to the other, and that's something to
9 look at.

10 DR. PORTIER: Any additionally
11 commenters? No? Dr. Lee.

12 DR. LEE: I just sort of have a
13 question. Reading through this particular
14 question, there's a bunch of it that I don't
15 think has been addressed in this discussion.
16 A lot of good points have been raised, but
17 when we have to answer question 2 tomorrow, we
18 need an idea about what is a duration of
19 interest, or an exposure window of interest.
20 And I'm not sure I've gotten much guidance
21 from this discussion on what sort of exposure
22 windows we should be considering tomorrow.

1 DR. PORTIER: Dr. Krishnan.

2 DR. KRISHNAN: Yes, I think most
3 of our consideration was the duration of
4 toxicological concern versus the frequency of
5 monitoring, so that, you know, the frequency
6 for monitoring somehow doesn't give us any
7 data in terms of relevance to the duration of
8 the toxicological effect concern. But based
9 on the toxicokinetic aspects that we heard, or
10 pharmacokinetic aspects we heard, so we tried
11 to answer it on the basis of pharmacokinetics
12 and some of the effects on precursors that
13 have been discussed.

14 But coming specifically to the
15 exposure window of interest, I think my
16 colleague to the left indicated that there's
17 no specific window that can be defined on the
18 basis of the available data. But I mean when
19 you think of the window of exposure, it
20 depends on the critical tox study though to
21 drive the point of departure assessment. At
22 least that's how I'm looking at it, maybe I

1 can get some clarification or help from the
2 others.

3 If the critical window of exposure
4 of the key studies that end up driving this
5 assessment have any specificity of a two-day
6 window during development or something like
7 that, that's how I see a window of
8 susceptibility and window of critical
9 exposure. And based on the discussions that
10 I have seen, it's more of the sustained effect
11 on the specific precursors that would appear
12 to have a key impact on the outcome.

13 And one of the figures in the
14 document, I thought it was Figure 2, where it
15 showed dose duration relationship as well for
16 effect on the LH surge. I forgot the page
17 number; it was Figure 2, that white paper --
18 27. Okay. So that one showed a dose duration
19 relationship for the NOEL from almost a single
20 day to about a six-month duration or so, which
21 essentially relates to the key event on LH
22 surge, which relates to the critical outcome.

1 So I mean we are kind of -- well,
2 at least from my perspective, from the studies
3 I have heard and seen, I am not getting any
4 other -- well, I don't have any other input.
5 Maybe we'll see if EPA wants to add some
6 clarification to that.

7 DR. LOWIT: Yes, I'll rephrase
8 maybe what Dr. Lee was thinking in my own
9 words. To go back to one of the things I
10 think Ken had sort of parked, the issue of the
11 duration, the acute versus chronic, I've got
12 open on the white paper, page 29, Table 3,
13 which is the early beginnings of what Penny
14 was mentioning around the temporal concordance
15 table for mode of action analysis.

16 It shows the currently -- or at
17 least as of two months ago, this is changing
18 fast -- the HPA data for ACTH and cort and
19 progesterone, and some GnRH four days, LH
20 across, one day up to 26 weeks, and some
21 cyclicality data from one day up to 26 weeks.
22 And keeping in mind that we're going to have

1 some better dose response to fill in a number
2 of those times.

3 I think it's relevant to think
4 about those durations, everything from that
5 one day cort measure all the way up to the
6 six-month LH endpoint that is the current
7 foundation of the RfD, and pretty anything
8 shorter or in between. It's open for us to
9 pick two days, four days, three and a half, or
10 seven and four-quarters, you know, it's --
11 four quarters, that eight -- but three-
12 quarters, you know, it's pretty much open to
13 choose whatever makes the most sense
14 biologically.

15 And what I haven't heard, and I'm
16 hoping we'll hear in the second half of the
17 question, is the dynamic considerations.
18 We've heard a lot of really good points around
19 the kinetic, but what we haven't talked about
20 in this question are the dynamic
21 considerations, the relationship of the key
22 events, the time required to go from changes

1 in cort to eventually changes in LH, and how
2 you think about those and how that becomes
3 relevant to humans, the translation of the
4 one-day to the four-day to the LH, and then
5 translating that into humans.

6 Those are the factors that I
7 haven't heard in this conversation that get at
8 I think what Dr. Lee is asking about.

9 DR. PORTIER: Dr. Krishnan.

10 DR. REED: Now I recall when I
11 came to the meeting, in reference to your
12 question, Dr. Lee, when I came to the meeting,
13 I said to myself the answer is very simple,
14 monitor every 15 minutes. That's what this
15 table tells me.

16 (Laughter.)

17 DR. KRISHNAN: And then as I went
18 along, as the discussions went along
19 yesterday, I think, before the end of the day,
20 I said, I think three or four days or so seems
21 more reasonable. And then I listened to Dr.
22 O'Byrne and then some of our own discussions,

1 and what I'm convinced is that, you know, the
2 key event essentially relates to a sustained
3 effect and it's all the area under the curve
4 either internally or externally.

5 That's where I stand right now.
6 And then so the duration is simply you just
7 multiply it with the number of days that you
8 want, and that's where I stand. So I wanted
9 to clarify that.

10 DR. PORTIER: Dr. Gilliom, and
11 then Dr. O'Byrne.

12 DR. GILLIOM: So you're getting,
13 you know, a few kind of outside-the-box
14 questions from hydrologists who don't
15 understand anything about, or statisticians,
16 about the toxicology, but we're getting into
17 how you translate the realities of the
18 exposure situation into what's relevant for
19 what ends up being a concentration benchmark.

20 And one of the questions I'm still
21 a little confused about, and it's kind of in
22 two parts, is one, and this might be an EPA

1 question, are we still considering the total
2 chlorinated triazine approach, or are we
3 talking only atrazine as a parent compound?
4 And I haven't heard much further discussion of
5 that.

6 And then second, you know, I think
7 with good reason we're thinking about the
8 actual temporal exposure conditions, both of
9 the variation in the water and the variation
10 of the ingestion that happens. But also what
11 we leave out, and it's probably an impossible
12 question but I've to bring it up, is how
13 comfortable is everyone with the conclusions
14 based on the atrazine functionality models and
15 so forth when you also know it's in the
16 presence of a lot of other contaminants?

17 And I guess maybe it goes to, more
18 than anything, I want some perspective on that
19 because it really affects how we view the
20 monitoring requirements. If it were important
21 to pick up certain coincident occurrences,
22 then they might have different patterns and we

1 would have to know how to factor that in to
2 characterizing that.

3 Now I know it adds probably and
4 impossible level of complexity, but
5 unfortunately it's kind of the reality of
6 what's out there, and that's why I bring it up
7 and look for some reaction.

8 DR. PORTIER: Dr. O'Byrne. Oh,
9 let Dr. Okana go next?

10 DR. AKANA: Akana, Okana, doesn't
11 matter.

12 (Laughter.)

13 DR. AKANA: Yesterday we saw a
14 slide from Dr. Handa that I thought could be
15 very useful here. He had a slide where he
16 withdrew atrazine so the animal -- seeing it
17 and then you saw the recovery. And I was
18 absolutely, first of all, thrilled to see it
19 was not irreversible, but second, if I
20 remember right, it declined in four days. So
21 an off response might be very helpful in
22 figuring out your window of vulnerability and

1 duration.

2 DR. O'BYRNE: In the context of
3 the surge, which seems to be the critical
4 event, it's not like a knee-jerk response.
5 This is a massively complicated neuroendocrine
6 signaling system which starts with a gradual
7 rise in estradiol resulting in cascades of
8 neuropeptide changes in the brain. And this
9 event takes probably a day or two to actually
10 get it to work.

11 It's triggered by a rise in
12 estradiol, and those levels of estradiol have
13 to be elevated at a critical level for many,
14 many hours, not two or three, we're talking in
15 women it's something like a day. Yes? And in
16 the context of rats, and they have a four-day
17 cycle, so the window is much, much shorter.
18 So that's one of the reasons why I caution
19 against comparing women with rats. I mean
20 it's just outrageous at many, many levels.

21 (Laughter.)

22 DR. O'BYRNE: We're talking about

1 neuroendocrinology here.

2 DR. PORTIER: I'm glad to hear
3 that. Glad to hear it.

4 DR. O'BYRNE: So I think in terms
5 of the duration, I think that -- I think it's
6 very difficult for you guys to appreciate the
7 duration in terms of sampling water and things
8 like that. I don't know how you're going to
9 do it, to be honest.

10 But this is an event that takes a
11 long time to kick start, and in some ways it's
12 astonishing that it takes four days of daily
13 atrazine at phenomenally high doses, and I
14 still don't like that, of 50 milligrams per
15 kilo to knock it out, and then there's no dose
16 dependent nature to that, which, I mean I'm
17 beginning to realize may not be terribly
18 surprising, I mean in terms of, you know, you
19 completely knock it out with 50, 200, 300 and
20 probably 1,000.

21 It's just either there or it's
22 not. That's what I see in terms of the

1 ovariectomized estrogen-primed animal, which
2 is a much easier model to deal with because
3 there you've got the response to estradiol is
4 being evaluated. Whereas if you take a
5 spontaneously ovulating rat, the machinery is
6 massively more complicated because you may be
7 interfering with the rise in estradiol, and we
8 don't know the dynamics. If the rise in
9 estradiol is less steep, is not maintained at
10 a certain critical value that may impact
11 markedly.

12 So the ovariectomized rat given
13 exogenous gonadal steroids to induce this
14 event is a much cleaner model, and that's the
15 one that has been used and shown at three days
16 is necessary to knock it out. So I don't know
17 if that's helpful at all.

18 DR. PORTIER: Dr. Lowit.

19 DR. LOWIT: If Ken would let me --
20 if we can push on that concept a little bit.
21 Let's say theoretically, theoretically, there
22 were some -- there were a data set linking

1 four days of atrazine to LH to the surge, it
2 got down to something short, in the rat, of
3 something as short as four -- three, four,
4 five days. How would you translate that?

5 DR. O'BYRNE: It's already at four
6 days.

7 DR. LOWIT: So how would you
8 translate those rat four days into human days?
9 What sort of scale are we talking about? Are
10 we also on the day scale, are we on the week
11 scale? On a month, because that's a whole
12 cycle?

13 DR. HORTON: Yes, I need a
14 refresher course. What happens to
15 corticosterone or cortisol in the rat when you
16 treated them with atrazine? I'm going to
17 brain dead at the moment.

18 DR. COOPER: Yes.

19 DR. HORTON: Okay.

20 DR. COOPER: When you dose them it
21 increases.

22 DR. HORTON: Okay. Cortico -

1 DR. COOPER: Corticosterone
2 increases.

3 DR. HORTON: Increases. Okay.
4 Because there's a very large body of data from
5 the '80s and '90s from the laboratory of Neena
6 Schwartz on the effect of steroids on LH and
7 FSH secretion that can give you information on
8 the time course of this, and treatment over
9 the course of five to ten days with
10 corticosteroids prior -- or just treatment
11 with corticosteroids can influence the
12 differential secretion of LH and FSH.

13 So that might help inform the
14 studies on the set up of atrazine, and also
15 give you some information on the length of
16 time if atrazine setting up the induction of
17 corticosterone, that if you have an effect of
18 atrazine that is inducing the HPA axis, and
19 then you need the exposure of the HPG axis to
20 the steroids to then have an influence on the
21 HPG axis, kind of what the sequence of events
22 would be. So you need to have that kind of

1 time course.

2 DR. COOPER: Yes, I'm familiar
3 with Neena Schwartz's work. And you're right,
4 but it's really hard to pin down some of those
5 durations, but that's the information I'm
6 getting, that maybe we have more limitations
7 from the basic literature than I thought.

8 Back to this dose though, I think
9 I got -- I want to just restate something with
10 the rise in estradiol. In, you know, in a
11 four-day rat estradiol starts to rise around
12 noontime of the day of diestrus 2 and it
13 continues to increase throughout the evening
14 and into proestrus, and that's where you start
15 to have all the dynamic changes that Dr.
16 O'Byrne was referring to.

17 We've monitored that in intact
18 animals under atrazine. We don't -- again,
19 that's -- a lot of these questions are there
20 and we're trying to get as many answers as we
21 can. And when you dose with atrazine from
22 estrus, diestrus 1, diestrus 2, and proestrus,

1 those four days, that's the exact same model
2 that was published in Fraites's paper, the
3 doses required to decrease the amplitude of
4 the LH surge at 1800 hours, the effective --
5 the LOEL in that study was 6.25, the NOEL we
6 got was 3 point whatever dose halves are.

7 So I think the notion that the
8 estrogen-primed animal, we started out and we
9 continue to work with the estrogen-primed
10 animal. I personally don't really think the
11 estrogen plus progesterone animal is really
12 useful at tox because of the potent signal
13 that P4 gives the pituitary -- I'm sorry, the
14 hypothalamic-pituitary control.

15 But so the two I like, and these
16 are personal preferences, right, is the
17 estrogen-primed female and the intact animal.
18 Now it takes a tremendous amount of effort to
19 do an intact female period. But because we
20 have unlimited taxpayers' resources, we --

21 (Laughter.)

22 DR. COOPER: No, I mean it's -- we

1 are -- over the -- you know, if you're frugal
2 enough and you're careful enough, you can
3 follow the animals and you can make -- the one
4 thing you have to do if you're following
5 cycles -- if you're doing an intact animal is,
6 number one, and this is really a problem in
7 tox studies, is to make sure your females are
8 cycling. And that's not always the case in a
9 lot of things we get to review.

10 So we make sure for two weeks that
11 these females show four-day cycles. Then we
12 initiate our treatment and then we follow
13 them, and we kill them -- we have killed them
14 every two hours from 6:00 a.m. in the morning
15 to proestrus throughout -- well, now two hours
16 after dark. So we have now a data set that's
17 quite complete.

18 And where we're now currently
19 picking apart that rise in estradiol, that
20 rise in progesterone which is just as
21 important in the afternoon, and then where --
22 now, think about this, we're trying to

1 evaluate the normal cycle in the animal, but
2 we're dosing them with a compound that we know
3 at some dose is going to disrupt the cycle, so
4 it gets really dicey to make sure that you're
5 dealing with treatment effects as opposed to
6 throwing out affected animals in this kind of
7 thing.

8 When all that's said and done, we
9 do have a LOEL and a dose response down to a
10 NOEL of 3.125 -- that's the right number --
11 and then we've looked at estradiol and
12 progesterone, we haven't finished the -- and
13 we're looking at ovulation and all the
14 different things that we can just to make sure
15 that we have that boxed in properly.

16 So I think the notion that we
17 need -- 3.25 and 6 I think are still probably
18 up there in terms of exposure. I'm not going
19 to say they're low doses, but in terms of the
20 literature anyway that's down there around
21 where our -- the current point of departure is
22 of 1.8, I think is the NOEL; that's pretty

1 close.

2 So what we were looking for was a
3 question -- to the answer to this question
4 given that kind of information. It took four
5 days to get there to have an effect on the
6 surge. Is that the kind of exposure that you
7 could say this is -- you know, these things,
8 if you're exposed at some sufficient level for
9 that long, it can be adverse, whether it's
10 through adrenal or direct on the pituitary --
11 hypothalamic-pituitary axis. So that's one of
12 the questions.

13 And then the other question is,
14 built into that, is if it's a single-day
15 exposure, and I think I've already this
16 answer, if it's single-day and it's adrenal
17 response, which we may end up with the same
18 dose response but it may be meaningless in
19 terms of an adverse outcome, we can't -- an
20 adverse outcome on adrenal, and I think I've
21 heard that from this panel one time, which is
22 good. I think that's good. But you still

1 need an adrenal axis.

2 So I think the question we're
3 getting at is, do you have advice on -- I
4 think I've already heard it, and that one day
5 is probably insufficient right now. So it's
6 not like some other chemicals where we can
7 dose once, wipe out the surge, and it causes
8 problems with ovulation, and it causes
9 problems if the animal becomes pregnant with
10 the embryo development and those kinds of
11 things.

12 So we do have one day exposure.
13 If it was for a reasonable period for time,
14 should you go -- you know, that's the question
15 that we're asking, or seeking advice on.

16 DR. O'BYRNE: Okay. Can I ask you
17 a question. Have you tried one, two and three
18 days, or was it just one and four?

19 DR. COOPER: Not yet.

20 DR. O'BYRNE: You haven't. You
21 haven't done that.

22 DR. COOPER: No, we've done one,

1 two -- oh, yes, we've --

2 DR. O'BYRNE: You have?

3 DR. COOPER: No. We've dosed for
4 one or one, two, three, four, but we haven't
5 had the opportunity yet to --

6 DR. O'BYRNE: And have you looked
7 at the dynamics of the estrogen change in
8 those animals that were dosed for four days?

9 DR. COOPER: Yes -- have we looked
10 at the entire --

11 DR. O'BYRNE: Yes.

12 DR. COOPER: No.

13 DR. O'BYRNE: On day one, two,
14 three, four?

15 DR. COOPER: Only from 6:00 a.m.
16 on pro to two hours after lights out, every
17 two hours. And we haven't found a change in
18 that hormone. We've seen changes at nine
19 o'clock after we dosed, because we dose 9:00
20 a.m. on proestrus as well, and we see changes
21 in progesterone and cort at 10:00.

22 DR. O'BYRNE: So progesterone is

1 attenuated?

2 DR. COOPER: No.

3 DR. O'BYRNE: It's increased?

4 DR. COOPER: Yes. At that -- it
5 increases at 10:00 and 11:00, drops back down,
6 then you see the afternoon rise, and it goes
7 right up to the same levels that we see in
8 control, you know, 60 milligrams per --
9 nanograms per millimeter, somewhere around
10 there.

11 DR. O'BYRNE: Because of course
12 that progesterone is probably coming from --
13 it's going to be coming from the adrenals.

14 DR. COOPER: Yes. And the other
15 thing is that -- and we've looked at uterine
16 growth in those animals and that's one of our
17 key criteria is that you want to make sure
18 that you're uterus, which goes from about 200
19 milligrams to almost a full gram over that
20 day, it really balloons up, you want to make
21 sure that they're responding because you don't
22 want to have an animal who's not showing that

1 kind of rise in estradiol because then she
2 wouldn't be proestrus. That was our
3 assumption.

4 DR. PORTIER: Dr. O'Byrne, is this
5 helping you kind of converge --

6 DR. O'BYRNE: Yes, I see --

7 DR. PORTIER: -- on a duration? I
8 mean it's fascinating to watch you guys talk
9 to each other, but I'm trying to figure out if
10 this is helping you converge to this duration
11 question.

12 DR. O'BYRNE: Well, the -- I mean
13 I think the four-day duration seems a
14 reasonable ballpark. The question of how we
15 relate this to the menstrual cycle, that's a
16 really difficult one to appreciate because I
17 think in the rat you only need a very short
18 period of raised estrogen to trigger this
19 surge, but you need it for days. I think it's
20 something like 30 -- no, no, no, for the
21 raised elevation -- the elevated levels of
22 estrogen in women is a day or two, I believe.

1 Yes. So I mean that's just massively
2 different.

3 So if you look at it from that
4 point of view, then you have to -- you know,
5 you can model that you need a much, much
6 longer duration of exposure to interfere with
7 that positive feedback effect of estrogen in
8 women. You've got to couple that with the
9 knowledge that the entire surge generating
10 mechanism in women and primates, higher
11 primates, is just totally different from a
12 rat. You don't even need a brain.

13 (Laughter.)

14 DR. O'BYRNE: You don't even need
15 a brain if you're a woman to have a surge.
16 It's an absolute truth.

17 DR. COOPER: Well, that's --

18 DR. O'BYRNE: The data is there --

19 DR. COOPER: -- I'm sorry --

20 DR. O'BYRNE: The data is there --

21 DR. COOPER: I understand Nobel,
22 sorry --

1 DR. O'BYRNE: The data is that it
2 would be estrogen -- the estradiol -- the
3 positive feedback effect of estradiol is the
4 pituitary phenomenon.

5 DR. COOPER: It's pituitary, in
6 the monkeys, Nobel's work, but I think there's
7 more than sufficient evidence to show that a
8 lot of chemicals that work essentially to
9 inhibitor or impair the pulsatile release of
10 GnRH and release of LH in humans. And I know
11 the pulse frequency is important, and it's --
12 just as well in humans.

13 But I think the -- back to the
14 duration question, I think we could scale that
15 up and scale it down, and I think that's part
16 of the issue. You're right.

17 DR. PORTIER: Dr. Schlenk.

18 DR. SCHLENK: Yes, just a simple
19 question. I mean do you know from your ex
20 vivo studies what tissue concentration you
21 need, say in the adrenal glands, to get a
22 cortisol release?

1 DR. COOPER: No, not now.

2 CHAIR HEERINGA: Steve Heeringa.

3 I think you've started to address what was
4 going through my mind, and statistically,
5 statistically, the most pathological case in
6 terms of these chemographs and exposures are
7 these short term surges we see, and we had a
8 couple of examples, the Missouri raw water
9 thing that we see where you have several
10 spikes in atrazine concentration in the raw
11 water supply, and they last for about two or
12 three days.

13 And in terms of thinking about the
14 coincidence of sort of the sampling frequency
15 we'll be talking tomorrow, and the concerns
16 you're talking about, it's the first of June,
17 Thursday, it rains, Sunday morning I make
18 coffee and I get a surge of atrazine in my
19 community water supply, if it happens that
20 fast. I make the same coffee Monday morning
21 and Tuesday morning. By Tuesday morning it's
22 gone, it's back down to a lower level.

1 I think what is the impact of that
2 maybe for me, or for women in the household,
3 et cetera. I think that's the key sort of
4 sampling issue that we need to get at. I
5 think if you're saying that it's sustained
6 concentrations at certain levels over a period
7 of time, the statistical issues will become a
8 lot easier.

9 But it's the -- and most of the
10 chemographs, and Nelson and others could
11 confirm this, that we saw, even in raw water,
12 there maybe are two peaks, two or three peaks
13 per year that are real spikes, and most of
14 them are much more uniform flat. And I assume
15 in finished water it even looks flatter yet,
16 so. But I think you were getting at that when
17 you were talking about this before.

18 DR. PORTIER: Dr. Williams.

19 DR. WILLIAMS: I just have one
20 comment about the female menstrual cycle. It
21 does take a much longer time than the rat to
22 actually create a menstrual cycle, but it's

1 not clear that it would take much longer or
2 potentially any longer at all to disrupt that.

3 So if you have an atrazine spike
4 that's the day before or two days before
5 you're going to have an LH surge, just for
6 that one day, could that be disruptive? Based
7 on all the central effects we've been talking
8 about is that enough to disrupt? It's
9 certainly not enough to create a menstrual
10 cycle, obviously you need the days and the
11 feedback and so forth, but how long does
12 disruption take?

13 DR. O'BYRNE: I think you're
14 perhaps asking the wrong person. I mean there
15 are experts in the US who know a great deal
16 more about the control of the menstrual cycle
17 in women. But I would be very surprised if
18 you perturbed the follicular phase by --
19 during that two-week period you perturbed it
20 on one particular day, I'd be amazed if it
21 impacted on that follicular phase. I'd be
22 absolutely astonished. It just wouldn't make

1 sense to me.

2 I'm just thinking of my time when
3 I was working with monkeys, you really do have
4 to make a major stressor to perturb the
5 menstrual cycle. I don't think one event
6 would make a jot of difference. And this was
7 in the context of restraining Rhesus monkeys
8 in primate chairs. It didn't disturb the
9 cycle. I think --

10 DR. PORTIER: Dr. Horton.

11 DR. O'BYRNE: -- it's quite -- I
12 think it's quite robust.

13 DR. HORTON: This is where I think
14 when we finally see epidemiological data and
15 kind of the absence of data on the
16 developmental issues comes into play because
17 it's in development that neuroendocrine
18 systems and neurotransmitter systems are much
19 more sensitive, and where exposure for
20 transient -- or exposure to chemicals for
21 transient periods of time can have serious
22 long term effects.

1 And so if you take a hit for a day
2 or two at just the right time of development,
3 and unfortunately because we're talking about
4 humans, we don't have experimental data on it,
5 and we never will have experimental data, and
6 you really can't extract it very well, even
7 from epidemiological data, but certainly
8 looking at rodent data, the work that's been
9 done with steroids, you know, treating them at
10 the right stage of the prenatal period for one
11 day with the right steroid can have major
12 developmental effects.

13 Most of this work was done looking
14 at the effects of sexual differentiation, but
15 we're now finding that different critical
16 periods exist for, say, treating with
17 androgens that results in changes in
18 metabolism later in life resulting in the
19 recapitulation of factors like metabolic
20 syndrome.

21 So I think taking into
22 consideration the possibility that exposure to

1 these pulses or periods for over a few days at
2 the wrong time of fetal development might be
3 important. Also what we haven't seen any data
4 on, and I don't know if this will addressed at
5 some other SAP, might be the -- whether there
6 are any data on impacts on in vitro
7 fertilization, early pregnancy, loss. If Dr.
8 Lowit would like to comment on whether any of
9 that is going to be addressed.

10 DR. PORTIER: Actually, before we
11 get to that, I think the hour's getting late.
12 We long ago wiped out my desire to have the
13 hydrology discussion.

14 What I wanted to suggest is if we
15 can capture some of these unanswered
16 questions, you know, the kind of things that
17 we've been -- we haven't had any answers, but
18 we've had some questions that I think will
19 help EPA to refocus how you think about
20 duration and, you know, some of the issues of
21 women's menstrual cycle, the level needed to
22 impact it, at least in higher primates, the

1 key reproductive and what we know about, if I
2 understood, steroidal impacts on key
3 reproductive and developmental points.

4 You know, if we can kind for ask
5 the right questions, that'll at least help the
6 EPA staff kind of begin to formulate the
7 answer. I don't think we quite have gotten to
8 your -- the answer to your questions, but I
9 don't think Dr. Lowit really expected an
10 answer to the question.

11 If that's agreeable? Any final
12 kind of concluding remarks on this point?
13 Dr. Krishnan.

14 DR. KRISHNAN: Could it be a
15 confusing remark?

16 DR. PORTIER: Huh?

17 DR. KRISHNAN: Could it be a
18 confusing remark rather than a concluding one?

19 (Laughter.)

20 DR. PORTIER: That would be an
21 additional confusing remark.

22 DR. KRISHNAN: Okay. I just want

1 to -- before we -- at least in mind I just
2 wanted to get a clarification. So as we see
3 these various precursors that are being
4 modified, you know, which is listed in Table
5 3 where we've got, you know, a change
6 occurring in 15 minutes in cort level, or over
7 a longer period the effect on LH surge and so
8 on, does that -- well, the way I see it is
9 that the monitoring frequency then has to
10 match with this, with essentially with each
11 one of these key event or precursor, whichever
12 you pick, so your frequency will have to match
13 that somehow.

14 But then not each one of these
15 precursors are going to make it through the
16 risk assessment. Like, you know, maybe the
17 cort level is not going to be used in
18 determining the PoD or something. So I think
19 that's where -- that's what has to get into
20 this equation to determine whether we need to
21 ask this question about these various
22 precursors and the frequency of monitoring.

1 Because if not all of these get
2 to -- get into the process of deriving -- or
3 driving the PoD, then I don't see that being
4 a critical factor in this consideration. I'll
5 leave it at that.

6 DR. PORTIER: Thank you.

7 I'm going to actually leave this
8 question open just in case somebody comes up
9 with a brilliant idea in the morning. There's
10 no reason to close it. But I think at this
11 point we're going to break for the day and
12 begin again tomorrow morning at 8:30 again
13 with kind of just a recapitulation of this,
14 and then we'll go into the discussion.

15 I'd like the hydrology people to
16 hang around for a few minutes here after the
17 meeting so we can talk strategy for tomorrow.

18 Thank you very much.

19 (Whereupon, at 4:51 p.m., the
20 meeting was adjourned, to reconvene at 8:30
21 a.m., Thursday, April 29, 2010.)
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